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THE SUGAR CONTENT OF THE CEREBRO-SPINAL FLUID AND ITS DIAGNOSTIC VALUE, ESPECIALLY IN ENCEPHALITIS LETHARGICA

By R. COOPE

(From the Department of Biochemistry, University of Liverpool)

I. *Introduction and Review of the Literature.*

It was in 1918 that encephalitis lethargica made its appearance in France, and many cases were reported, mainly in the *Bull. et mém. Soc. méd. des hôp. de Paris.* The earliest description of the disease noted that the cerebro-spinal fluid was approximately normal—clear, under slight pressure, with a normal cell content, no excess of protein, and a normal reduction of Fehling's solution. In the later epidemic of 1919–20, however, a close study by observers such as Netter, Achard, Pierre Marie, Widal, Bénard, and others, showed that in many cases there were definite abnormalities. A lymphocytosis was frequently found. In some cases an excess of protein occurred, in others the amount was normal.

Early in 1920 several observers stated that the fluid had an abnormally high sugar content. Netter recalled the fact that in 1898 he had seen this phenomenon in cases of tumours near the cerebellar peduncles, and he described six cases of encephalitis lethargica in which the sugar content of the cerebro-spinal fluid varied from 70 to 97 mg. per 100 c.c., with an average of 86 mg. Laporte and Rouzaud reported twelve cases, with sugar varying from 66 to 101 mg. per 100 c.c., with an average of 88 mg. Pierre Marie and Mestrezat made an extensive chemical investigation of the cerebro-spinal fluid in one of their cases, and found a sugar content of 94 mg. per 100 c.c., as against a normal content of 53 mg. They contrasted this with the low figure usually found in tuberculous meningitis. Dopter also described a case in which the sugar content of the fluid was 85 mg., and emphasized the great diagnostic importance of this finding, particularly in the differentiation of encephalitis lethargica from acute or tuberculous meningitis; it was not, however, pathognomonic of, nor indeed always constant in, encephalitis lethargica.

In spite of this reservation, it was evidently felt that here was a most valuable laboratory finding for diagnosis. In an article on 'The Cerebro-spinal Fluid in Encephalitis Lethargica', Bénard undoubtedly reflected the prevalent French opinion on the matter in his summary—'l'hyperglycorachie n'est pas

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constante. Par sa grande fréquence, elle constitue un signe de haute valeur et qui peut être d'un sérieux appoint pour le diagnostic. Elle varie de 0 gr. 67 à 1 gr. 06 par litre.'

Throughout 1920, reports of cases continued to appear in the French journals. The great majority of the cases reported showed a 'high sugar content', though a not inconsiderable number were normal in this respect. I have found ninety-two cases in the literature where definite figures are given (see Table I). Of these seventeen show figures of 55 mg. or less—roughly 18 per cent. of the cases.

Netter and Dopter had already mentioned other conditions in which the sugar content might be 'high'; other authors, directly or indirectly, emphasized this. Fiessinger and Janet described three cases simulating encephalitis lethargica in which the post-mortem showed no lesion in the mesencephalon itself: (i) diffuse sarcomatosis, with a sarcoma in the basilar process of the sphenoid, pressing on the mesencephalon—sugar content of fluid 103 mg. per 100 c.c., later 293 mg.; (ii) meningeal haemorrhage—sugar content 95 mg., later 115 mg.; and (iii) terminal meningeal miliary tubercles (not a primary tuberculous meningitis)—sugar content of fluid 180 mg., no glycosuria. Achard and Rouillard noted a case of mesencephalic syphilis simulating encephalitis lethargica, in which the sugar content on two examinations was 75 and 70 mg. per 100 c.c. respectively. De Laverge reported a number of cases of post-diphtheritic palsies with polyneuritis and paralysis of the palate. The figures are 'high', and are shown in Table I, for comparison with those of encephalitis lethargica. Finally Rouquier gives figures from sixteen cases of convulsive or motor troubles of pithiatic origin. I have shown these also in Table I for comparison, and it will be seen that in ten cases the sugar content is above 70 mg. per 100 c.c. The same author, in conjunction with Bénard, also reported a case of hysterical narcolepsy in which the sugar content was 72 and 74 mg.

It is unfortunate that in all but two papers the method of estimating the sugar is not mentioned, and hence any strict comparisons of the figures may not be justifiable. Rouquier appears to have used Bertrand's ferrous sulphate and potassium permanganate method. Rivet and Lipschitz, in one case of epidemic hiccough followed by encephalitis, used 'Folin's method' and obtained a result of 72 mg.

Another difficulty lies in the absence of any definite agreement as to what constitutes a normal sugar content of cerebro-spinal fluid. French workers appear to accept Mestrezat's figure of 48 to 53 mg. per 100 c.c., based on an examination of twenty cases. Unfortunately we have been unable to find a description of his method. Nawratzki (1897), using Allihn's method, found an average 'normal content' of 46 mg. per 100 c.c. Von Jaksch (1909) in twenty normal cases found an average of 60 to 80 mg. Kopetsky (1913), using Benedict's method, in eight cases also found an average of 46 mg. A. H. Hopkins (1915)—from whose paper these figures for 'normals' are taken—using a modified Bang's micro-method over 'a series of normals', found 60 to 75 mg.; Kraus

and Corneille, 80 mg. Neuberg states that the cerebro-spinal fluid contained the same amount of sugar as the blood; Hopkins thinks that it usually contains about 10 mg. less per 100 c.c., although the actual figures which he gives in his paper show very marked variations.

The general opinion of workers in this field appears to be that the sugar content of the cerebro-spinal fluid varies with that of the blood, though the variations are not so great as those of the blood. Weston, using the method of Myers and Bailey, investigated the sugar content of both blood and cerebro-spinal fluid in a series of asylum patients suffering from various types of insanity. The average of his figures for cerebro-spinal fluid lies roughly between 60 to 70 mg., and for blood between 100 and 120 mg., with a general difference of about 45 mg. per 100 c.c. Whether samples of blood and fluid were taken at the same time is not stated—possibly an important matter, when the variations in the sugar content of the blood before and after ingestion of carbohydrate food are considered. At all events, if the figures which he gives in his various tables are plotted as curves, a rough parallelism between the sugar content of the blood and that of the cerebro-spinal fluid is evident in most of his series. The average figures for these insane cases are well above the French 'normal'. Hopkins also found figures which French workers would term 'high' in many types of cases—general infections, such as pneumonia (without meningitis), intoxications (morphia, acetanilide), diabetes, nephritis, and various nervous diseases.

Two definite points thus emerge from a study of the literature. In the first place, a 'high' sugar content should not be regarded as a positive diagnostic sign of encephalitis lethargica—a position which the early French workers such as Dopter were careful to take; in the second place, a low sugar content (provided the fluid is fresh) is a very strong indication of an acute or tuberculous meningitis. The cases taken from Hopkins's paper (Table I) are of great interest from this point of view, and contradict Boyd's view, in his book on the cerebro-spinal fluid, that the sugar content is not diminished in tuberculous meningitis.[1]

II. *Author's Results and Conclusions.*

The findings in my own series of 95 cerebro-spinal fluids confirm the above conclusions. It has not been possible simultaneously to examine the sugar content of the blood.

Desirable as it is, for purposes of comparison, to obtain the fluid of normal

[1] As this paper goes to press, I note the appearance of a paper by Foster, giving his results in 11 cases of encephalitis lethargica (*Journ. Amer. Med. Assoc.*, lxxvi, May 7, 1921, p. 1300). He finds a sugar content ranging from 53 to 113 mg. per c.c. of cerebro-spinal fluid, with an average of 76 mg. The average of my series is 74 mg. per 100 c.c. However, as he puts the normal figure at 53 mg. (22 cases with figures varying from 44 to 61 mg. per 100 c.c.), he thinks that 'hyperglycorachia' is usually present in encephalitis lethargica.

persons, this is, for obvious reasons, not feasible. In this series of cases, however, lumbar puncture was done on three cases with symptoms which had erroneously suggested organic nervous disease. In one case of persistent headache, thought later to be of hysterical origin, a 'normal' fluid was withdrawn, containing 64 mg. of sugar per 100 c.c. Another case with transient inequality of pupils, diagnosed wrongly as an early case of tabes, showed a 'normal' fluid with a sugar content of 83 mg. per 100 c.c. The third case had a transient lethargy; a 'normal' fluid was withdrawn, containing 69 mg. of sugar per 100 c.c.

Method. The method used was that described by Folin and Wu for the sugar of blood. 1 c.c. of cerebro-spinal fluid was taken in an ordinary clean, dry test-tube and diluted with 7 c.c. of distilled water; 1 c.c. each of 10 per cent. sodium tungstate solution and of $\frac{2}{3}$ N. sulphuric acid was added. The test-tube was shaken vigorously and left to stand for a minute or two until the protein was precipitated. The fluid was then filtered through starch-free filter-paper (Whatman No. 44); in the presence of an excess of protein two layers were usually necessary. 2 c.c. of the filtrate were taken and the sugar estimated as described in Folin and Wu's paper. We have always tested some of the remaining filtrate with salicylsulphonic acid, in order to make sure that the precipitation of the protein had been complete. The fluids should be examined as fresh as possible. Contamination with certain types of bacteria may considerably reduce the sugar content, if the specimen is at all stale.

The sugar content (per 100 c.c.) obtained in the various cases is as follows :- -

Encephalitis lethargica,[2] 85, 94, 68, 83, 67, 91, 69, 54, 80, 54, 72 mg.

Tuberculous meningitis, 40, 29, 55, 24, 24, 23, 25, 26, 36, 14, (59),[3] 22, 18 mg.

Pneumococcal meningitis, 19 mg.

Meningococcal meningitis, 8 mg.

Other diseases:

Uraemia, 87 mg.

Pneumonia (without meningitis), 63 mg.

Hydrocephalus, 63 mg.

Syphilitic meningitis, 100, 91, 80, 72 mg.

Tabes, 61, 54, 78, 72 mg.

General paralysis of the insane, 102, 62, 78, 48, 44, 54, 63, 83, 67, 50 mg.

Mania, 87, 85, 83 mg.

Epileptic insanity, 78, 72, 72, 78 mg.

Imbecility, 111 mg.

Dementia praecox, 74, 63, 56, 78, 72, 81, 74, 73, 72, 67, 68, 74, 61, 61, 63 mg.

Delusional insanities, 73, 77, 80, 72, 89, 73, 66, 68, 66, 61, 74, 81, 74, 51, 43, 63, 63 mg.

[2] Only cases where the diagnosis has appeared reasonably certain have been included.

[3] A doubtful case. Tubercle bacilli not found. Death 36 hours after admission to hospital. Post-mortem refused.

Paranoid dementia, 91 mg.
Disseminated sclerosis, 61 mg.
Cerebellar atrophy, 65 mg.
Cases not diagnosed, 50, 63 mg.
'*Normals*', 64, 69, 83 mg.

The cases have been divided into three groups, and they are classified according to their sugar content in Table II. It will be seen that many of the cases in the third group show figures quite as high as those of encephalitis lethargica. There is, moreover, a striking contrast between all these figures and the low figures of tuberculous and other acute meningites. It is, perhaps, worth noting here that even in the fluids with a low sugar content, whenever, as was often the case, I have boiled some of the original fluid with Fehling's solution and left it to stand for some minutes, there was invariably a reduction, as shown by the presence of small red granules of cuprous oxide at the bottom of the tube. This occurred even in the case with the low content of 19 mg. per 100 c.c. It is obvious, therefore, that the rough qualitative method so frequently used is of little value. In two of the cases of tuberculous meningitis the bacilli were not found in the fluid, but a low sugar content was present, 23 and 24 mg. per 100 c.c. respectively; the post-mortem in each case confirmed the diagnosis.

My own observations thus confirm the conclusions drawn from a survey of the literature of the subject, and further show that it is extremely probable that the 'normal' figure of Mestrezat is too low. At all events, the sugar content usually met with in most cerebro-spinal fluids obtained for diagnostic purposes, when estimated by a reliable method, lies between 60 and 80 mg. per 100 c.c., thus agreeing with both von Jaksch's and Hopkins's figures for 'normals'.

On the other hand, a low sugar content, especially one below 40 mg. per 100 c.c., is strongly in favour of a meningitis whose casual agent is some organism that can consume or destroy sugar—provided, of course, that the specimen is not contaminated or stale. In this connexion a sugar estimation may be of great value in differentiating particularly between encephalitis lethargica and tuberculous meningitis—a differentiation which clinically is not always easy in cases where the tubercle bacillus has not been found in the fluid.

Two cases are given to illustrate this point.

Case I. M. W., aged 13, admitted 17.2.21 to the Royal Infirmary, complaining of drowsiness and 'seeing double'. She had been ill for a fortnight before admission, with marked constipation, diplopia, and drowsiness.

She came of a tubercular family, the mother having had hip disease, and an uncle a tuberculous knee.

On admission, temperature was 99·6° F., rising in a few hours to 102° F.; compressible pulse, 114 to the minute. Face sallow, mouth dry, with slight bleeding from the gums, the throat coated with stringy mucus. The abdomen was rather tumid, not tender; liver and spleen not palpable.

Headache was absent, but there was marked lethargy; she would answer 'yes' or 'no' to questions, if she were roused. No twitchings, no convulsions. Slight rigidity of lower limbs, catatonia of both arms. Kernig's sign positive. Ophthalmoparesis, with slight external strabismus, and slight lateral nystagmus

present. The pupils reacted sluggishly to light and accommodation. Fundi normal. Marked double ptosis. She could not protrude the tongue beyond the teeth. No head retraction; incontinence of urine was present; constipation was severe. There was no ankle clonus or Babinski sign; abdominal reflexes were absent, and the right knee-jerk was a little exaggerated. Sensation was apparently normal. There was some wasting.

On examination of the lungs, occasional coarse rhonchi were to be heard all over the back of the chest.

Lumbar puncture gave a clear fluid, not under pressure. There was no coagulum, no excess of protein, but a slight excess of small lymphocytes (15 per c.mm.). Wassermann negative. The sugar content was 91 mg. per 100 c.c.

Later, she developed small rapid tremor of the upper extremities and the facial muscles, particularly the orbiculares palpebrarum. The pupils became dilated, and there was incontinence of faeces as well as of urine. At the same time, the ocular palsies disappeared, and the patient became less lethargic.

In view of the history of tuberculosis in the family, it was thought at first that the case was probably a tuberculous meningitis. The sugar content of the cerebro-spinal fluid was against this diagnosis, and the subsequent progress of the case was that of an encephalitis lethargica. The patient recovered completely and was discharged on May 2, 1921.

Case II. A. B., aged 4 years, admitted to the Royal Liverpool Children's Hospital 18.4.21, complaining of sleepiness. Three weeks before he was disinclined to play, and had severe headache. He became very sleepy; was constipated during the illness. There was no vomiting, but slight cough.

On examination, the child kept his eyes half closed. Upper lids swollen. Very drowsy, he would fall asleep feeding himself. He appeared to hear what was said, and made simple movements, but had to be roused constantly. The eyes reacted to light: there was some internal strabismus of right eye. The disks were normal. Knee-jerks were active, Babinski's sign negative, abdominal reflexes present.

A week later the child seemed improved and was less drowsy, and the diagnosis of encephalitis lethargica was made. Six days later, however, after being allowed up, he vomited for no apparent reason. The vomiting persisted and a lumbar puncture was done. The fluid was under pressure, clear, and without a coagulum. There was an excess of protein, a lymphocytosis (44 cells per c.mm.), and neither tubercle bacilli nor other micro-organisms were found. The sugar content, however, was only 36 mg. per 100 c.c., and consequently a diagnosis of tuberculous meningitis was suggested.

The child continued to vomit, wasted rapidly, and developed a temperature of 100° to 101° F. Later, Kernig's sign was present; ankle clonus and Babinski's sign occurred in both lower limbs. There appeared a well-marked tâche cérébrale, retraction of the abdomen, and inequality of the pupils, with failure to react to light. On May 13 the child became very cyanosed, and had attacks of Cheyne-Stokes breathing. There was no head retraction, but the right arm and leg were stiff, the wrist acutely flexed, the finger-tips approximated, and the toes kept pointed. The temperature rose steadily to 105° F., and the pulse became thin and rapid. Death occurred the next day.

A post-mortem was refused; but the diagnosis of tuberculous meningitis was borne out by the progress of the case.

Unfortunately, comparatively few cerebro-spinal fluids come into the hands of any single laboratory worker, particularly those from diseases such as encephalitis lethargica or acute meningitis. As regards the significance of a low sugar content, however, the findings in this series of cases agree with the results of Hopkins and others.

Summary.

(1) The sugar content of the cerebro-spinal fluid from cases of encephalitis and of other diseases has been investigated.

(2) The French tendency to regard a 'high sugar content' as in favour of encephalitis lethargica does not appear to be justified, as figures quite as high occur in many other nervous diseases.

(3) A low sugar content, especially one below 40 mg. per 100 c.c., is strongly in favour of an infective meningitis.

(4) An investigation of the sugar content of the cerebro-spinal fluid by an accurate quantitative method is especially valuable in cases of tuberculous meningitis.

My thanks are due to many colleagues who have kindly provided me with material—to Professor Beattie and Dr. L. S. Ashcroft, of the Bacteriological Department, University of Liverpool; to Dr. Rundle and Dr. Hodgson, of Fazakerley City Hospital; and to Dr. Douglas Bigland, who has passed on much material from Rainhill Asylum. I wish especially to thank Dr. J. Hill Abram, of the Royal Infirmary, who suggested the work, and has taken a keen interest in its progress.

TABLE I. *Cases taken from the Literature.*

Mg. of Sugar per 100 c.c. Cerebro-spinal Fluid.	92 cases of Encephalitis Lethargica.	11 cases of Post-diphtheritic Palsies (de Laverge).	18 cases of Hysteria (Rouquier; Rouquier & Bénard).	3 cases of Pneumonia, no Meningitis (Netter, Bloch, & Dekeuver).	27 cases of Tuberculous and Acute Meningites (Hopkins).	55 cases of Nervous Diseases (Hopkins).
100–110	7 cases	1 case	—	—	—	4 cases
90–99	13 ,,	2 ,,	4 cases	1 case	—	4 ,,
80–89	25 ,,	2 ,,	2 ,,	1 ,,	—	11 ,,
70–79	20 ,,	4 ,,	6 ,,	—	—	12 ,,
60–69	8 ,,	2 ,,	2 ,,	1 ,,	1 case	14 ,,
50–59	12 ,,	—	3 ,,	—	1 ,,	5 ,,
40–49	6 ,,	—	1 ,,	—	4 ,,	3 ,,
30–39	1 ,,	—	—	—	10 ,,	1 ,,
20–29	—	—	—	—	5 ,,	1 ,,
10–19	—	—	—	—	5 ,,	—
0–9	—	—	—	—	—	—

TABLE II. *Author's Cases.*

Mg. of Sugar per 100 c.c. Cerebro-spinal Fluid.	11 cases of Encephalitis Lethargica.	15 cases of Tuberculous and Acute Meningites.	69 cases of other Diseases, chiefly Insanities.
100–110	—	—	3 cases
90–99	2 cases	—	2 ,,
80–89	3 ,,	—	11 ,,
70–79	1 ,,	—	21 ,,
60–69	3 ,,	—	23 ,,
50–59	2 ,,	1+(?) 1	6 ,,
40–49	—	1 case	3 ,,
30–39	—	1 ,,	—
20–29	—	7 ,,	—
10–19	—	3 ,,	—
0–9	—	1 ,,	—

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OBSERVATIONS ON THE PERCENTAGE OF SUGAR IN THE BLOOD OF ATROPHIC INFANTS[1]

By R. A. GUY

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THE marasmic or atrophic infant is apparently in a state of partial starvation. Although food adequate for maintenance and growth is introduced into the gastro-intestinal tract, he fails to thrive and gain in weight. No cause has been found for this failure.

Protein absorption from the intestine (except where there is diarrhoea) and nitrogen excretion in the urine have been shown to be practically normal (1, 2). Hutchison (3) has shown too that fat digestion and absorption are essentially normal, and recently Fleming (4), in an investigation of the respiratory exchange in atrophic infants, has found nothing to suggest that either fats or carbohydrates are not used in the ordinary way. Mattill, Mayer, and Sauer (5), by parenteral injections of glucose, find that the so-called carbohydrate tolerance, i.e. the amount of sugar which can be 'tolerated' without increasing glycuresis, is also within normal limits, and Fleming (4), by feeding glucose to atrophic infants, has shown that as much as 3 grm. per kilo body weight can be taken without increasing glycuresis. It may therefore be assumed that if carbohydrates are properly absorbed they can be utilized by the atrophic infant. The important question is, are the carbohydrates normally absorbed? The present observations were made in the hope that the sugar content of the blood might give an indication of absorption.

Normal Percentage of Sugar in the Blood.

In the normal adult the percentage of blood-sugar is found to vary from 0·065 to 0·170 depending on the interval after the ingestion of a meal. The usual 'fasting average' is given as 0·090 to 0·1. There is a rise after the ingestion of a mixed meal, and a quicker and higher rise after partaking of pure carbohydrate, with a subsequent fall to the fasting level within three or four hours. Most authors find that the normal rise exceeds 0·170 per cent., and conclude that if the

[1] This investigation was carried out under the auspices of the Child Life Investigation Committee of the Medical Research Council, by whom the expenses were defrayed.

liver, pancreas, and kidneys are functioning properly, the normal storing and eliminating mechanisms prevent a greater amount of sugar from accumulating in the general circulation. Prolonged periods of fasting in both man and animals have not produced a decrease in blood-sugar beyond that reached three or four hours after a meal.

In the normal infant the same general relationships have been observed. A post-prandial rise occurs, and is followed, during the next three or four hours, by a return to the 'fasting level', at which it remains even after prolonged starvation. In infants, however, greater individual variations are found, and the general level is lower than in the adult.

Table I is a summary of the observations made by previous workers in the healthy infant.

TABLE I.

Blood-sugar in Normal Infants. Blood taken Three or more Hours after Food.

Authors.	Method.	Average % of Sugar in Blood.	Remarks.
Cobliner (12)	Moeckel-Frank	0·07–0·14 (25 cases)	
Götzky (14)	Bang	0·077	
Bing and Wendelöw (15)	Bang	0·13	
Mogwitz (16)	Bang	0·07–0·11	Same for venous and mixed blood. Same after disturbance
Frank and Mehlhorn (17)	Bang	0·085	
Bergmark (18)	Bang	0·08–0·09	8 hours after food
Niemann (19)	Bang	0·079	0·0795, 8 hours after food
Cannata (20)	Lewis-Benedict	0·074–0·10	During first 24 hours of life
Sedgwick and Ziegler (13)	Lewis-Benedict	0·06–0·11 (46 cases)	During first 24 hours of life

It would appear from the above that the 'fasting values' are slightly lower than in the adult, although the individual variations are somewhat greater. Percentages of 0·06 to 0·11 may be considered normal.

Percentage of Sugar in the Blood in Pathological Conditions in Infancy.

In pathological conditions a few observations have been published. These have been summarized in Table II.

TABLE II.

Blood taken Three Hours after Food.

Disease.	Blood-sugar.	Authors.
Simple disturbances	No change	Cobliner (12) Mogwitz (16)
Enteritis	Increase	Bing and Wendelöw (15) Niemann (19) Chapin and Meyers (21) Götzky (14), Mogwitz (16)
'Intoxication'	(6 cases) 0·07–0·13	Cobliner (12)
	(8 cases) 0·08–0·11	Chapin and Meyers (21)
Atrophy 'decomposition'	(9 cases) 0·04–0·07	Cobliner (12)
	(1 case) 0·046	Chapin and Meyers (21)

In the conditions diagnosed as 'atrophy' or 'decomposition' a hypoglycaemia has usually been observed. Cobliner (12), Bing and Wendelöw (15), Mogwitz (16), and Rolly (22) have also noted a slight increase in the blood-sugar during pyrexia, a fact previously observed in adults.

Methods.

In the present investigations blood-sugar was estimated according to the Lewis-Benedict method as modified by Meyers and Bailey (23). The bicarbonate reserve of the plasma was done according to the 'micro-method' of Van Slyke (24). The blood was taken by the investigator from the superior longitudinal sinus directly into a glass syringe containing a few grains (about 0·5 per cent. of the weight of the blood drawn) of potassium oxalate. By using the sinus, changes in the blood due to stasis and crying were obviated. The blood was transferred to a centrifugalized tube, 2 c.c. were quickly removed by a graduated pipette for sugar estimation, and the remainder centrifugalized at once and the plasma used for the bicarbonate estimation.

That portion of blood (2 c.c.) removed for sugar analysis was laked with 8 c.c. of distilled water. To the 10 c.c. of laked blood approximately 0·5 grm. of powdered picric acid was added, and the mixture thoroughly shaken to ensure precipitation of the protein and complete saturation, with the production of a homogeneous dull yellow colour. After a few moments' standing this was centrifugalized for 20 minutes. The supernatant fluid was filtered and 3 c.c. were transferred to an ordinary test-tube; 1 c.c. of a 20 per cent. sodium carbonate solution was added, and the whole heated in the water bath for 15 minutes. Upon cooling to room temperature the solution was compared in the Dubosq colorimeter with the standard. As standard a stock solution of 0·02 per cent. pure glucose saturated with picric acid and kept in a dark well-stoppered bottle was employed. 3 c.c. of this solution plus 1 c.c. of the sodium carbonate were placed in a test-tube of the same calibre as that used for the blood filtrate and heated with it on the water bath. At intervals the standard was checked by a 0·02 per cent. solution of pure glucose, treated exactly as the blood filtrate. These two standards showed a constant agreement during three months. All analyses were made immediately upon obtaining the blood and the colorimetric observations determined within 2 hours.

Normal Percentage of Sugar in the Blood of Infants.

The blood of 43 normal infants was examined. They were all vigorous breast-fed children from one to twelve months of age brought to the dispensary for circumcision. Obviously, in the circumstances the time interval since the last feeding was not accurately known and the figures relative to this point are only approximate. The data are presented in Table III.

TABLE III.

Blood-sugar in Normal Infants.

No.	Age.	Blood-sugar.	Hours after Food.
24	7/52	0·1	at once
25	5/52	0·1	,,
19	3/12	0·07	,,
16	4/12	0·110	,,
33	5/12	0·072	,,
Average		0·090	
42	4/12	0·100	1 hour
8	6/12	0·071	1 ,,
9	6/12	0·066	1 ,,
10	6/52	0·07	1 ,,
Average		0·076	
27	12/12	0·072	1½ hours
17	11/52	0·100	1½ ,,
Average		0·086	
1	4/12	0·083	2 hours
23	4/12	0·070	2 ,,
12	5/12	0·090	2 ,,
28	12/12	0·083	2 ,,
2	1/12	0·076	2 ,,
5	5/52	0·086	2 ,,
1	6/52	0·066	2 ,,
3	2/12	0·090	2 ,,
18	9/52	0·100	2 ,,
4	3/12	0·066	2 ,,
11	3/12	0·140	2 ,,
Average		0·086	
41	7/52	0·680	2½ hours
43	6/52	0·082	2½ ,,
30	2/12	0·072	2½ ,,
20	9/52	0·100	2½ ,,
29	8/12	0·100	2½ ,,
Average		0·086	
22	1/12	0·060	3 hours
15	7/52	0·090	3 ,,
6	2/12	0·083	3 ,,
21	11/52	0·084	3 ,,
14	3/12	0·090	3 ,,
37	6/12	0·072	3 ,,
38	6/12	0·073	3½ ,,
40	6/12	0·066	3½ ,,
31	12/12	0·072	3½ ,,
36	2/12	0·063	3½ ,,
32	5/12	0·071	4 ,,
Average		0·0685	
39	5/52	0·073	4½ hours
26	12/12	0·080	5 ,,
34	3/12	0·073	11 ,,
35	3/12	0·070	12 ,,

No constant variation with age is observed. In the group taken three to four hours after the last feeding, the percentages range from 0·060 to 0·090 with an average of 0·068. In the present investigation then, the normal average with the modified Lewis-Benedict method is found to be lower than that observed by previous investigators using either the Moeckel-Frank, the Bang, or the Lewis-Benedict technique.

Percentage of Sugar in the Blood of Atrophic Infants.

Thirty blood-sugar determinations were made in eighteen different atrophic infants. The observations are summarized in Tables IV and V and the Chart.

Although almost all of the infants are less than 65 per cent. of their expected weight, the percentages of blood-sugar fall between 0·06 and 0·08, that is, within normal limits, with the exception of the six cases discussed below, not uncomplicated marasmus, which were vomiting on the day of analysis.

Only six cases show blood-sugars of less than 0·06 per cent., which may be considered as the lower limit of normal. However, as compared with 0·068 per cent., the general average normal level, the blood of the atrophic infant tends to

have a low percentage of sugar. This cannot be shown to have a constant relation to the percentage of the expected weight of the infant, nor to the weight trend, as has been suggested by Niemann (19).

TABLE IV.

Atrophic Infants. Blood taken 3–4 Hours after Food.

No.	Age.	Weight in Grm.	Percentage of Expected Weight.	Trend.	Calories per Kilo.	Calories per Expected Kilo.	Grm. of Carbohydrates per 24 Hours.	Blood-sugar, L.-B. Test.	Plasma Bicarbonate, Van Slyke Test.	Diagnosis and Results.		
7	3/12	2836	54	L	126	68	35·76	0·037	38·0	'Intoxication.'	V	Died
8	4/12	2780	47	G	125	60	53·02	0·041		Pylorospasm.	V	Well
	4/12	2752	47	G	148	70	65·78	0·043	50·7	Pylorospasm.	V	Well
18	8/12	4478	48	G	118	70	51·73	0·045	52·0	Pylorospasm.	V	Well
6	5/12	3940	58	G	153	90	86·7	0·050	61·2	Colitis.	V	Well
36	3/12	4226	81	S	118	95	54·6	0·050	50·7	Pylorospasm.	V	Well
9	2/12	2270	50	L	96	47	21·9	0·051	37·6	'Intoxication.'	V	Died
	2/12	2522	56	L	159	88	52·4	0·059	34·2	'Intoxication.'	V	Died
2	6/12	3032	41	S	104	45	14·6	0·060	64·3	Marasmus.		Well
21	8/12	4366	55	G	110	61	41·86	0·060	56·0	Marasmus.		Well
13	7/12	3912	52	L	93	40	22·68	0·062	44·9	'Intoxication.'		Died
1	4/12	2752	48	G	149	92	77·72	0·062	67·0	Marasmus.		*Died
10	3/12	4024	77	G	112	86	42·8	0·062		Marasmus.		Well
6	5/12	3800	59	L	93	55	35·76	0·064	49·7	Colitis.		Well
5	4/12	2690	49	G	184	88	38·34	0·064	47·3	Marasmus.		Well
15	4/12	2724	47	L	63	29	7·9	0·064	64·2†	'Intoxication.'		Died
4	5/12	3884	64	G	126	82	54·24	0·065	48·7	Marasmus.		Well
	4/12	3866	66	G	78	52	23·76	0·067	55·3	Marasmus.		Well
5	3/12	2288	44	G	135	60	33·69	0·066	48·6	Marasmus.		Well
13	6/12	3986	56	G	33	19	6·1	0·066	70·0	Marasmus.		Died
12	3/12	2690	50	G	97	49	11·76	0·066		Marasmus.		Well
1	3/12	2586	50	L	136	68	35·76	0·068	61·4	Marasmus.		†Died
3	6/12	3912	54	G	65	36	11·76	0·069		'Intoxication.'		Died
1	5/12	2892	45	G	153	69	42·24	0·071	57·4	Marasmus.		†Died
6	6/12	4142	59	G	119	70	37·8	0·071	52·6	Colitis.		Well
38	3/12	4478	86	L	95	80	38·88	0·072	55·0	Marasmus.		Well
3	7/12	4596	61	L	107	65	37·8	0·074	65·8†	'Intoxication.'		Died
12	5/12	2836	54	G	142	77	47·76	0·075	57·1	'Intoxication.'		Died
21	8/12	4366	55	G	110	61	41·86	0·076		Marasmus.		Well
37	8/12	6810	86	G	97	83	64·64	0·100	62·4	Marasmus.		Well

V Indicates that the infant was vomiting during day on which blood was analysed.
* Died of traumatic peritonitis.
† Patient was receiving sodium bicarbonate therapy.
G Gaining weight.
L Losing weight.
S Stationary.

In the six cases which showed markedly low blood-sugars, the only common factor observed was vomiting during the day on which the analyses were made. They were all receiving abundant carbohydrate in a diet of fair caloric value. The cases of intoxication and colitis had diarrhoea, those of pylorospasm were constipated, but neither diarrhoea nor constipation was more severe than in other cases. There would, therefore, seem to be some relationship between vomiting and a low percentage of sugar in the blood. The bicarbonate reserve

of the plasma does not vary either directly or inversely with the sugar content of the blood or the percentage of the expected weight of the infant.

TABLE V.

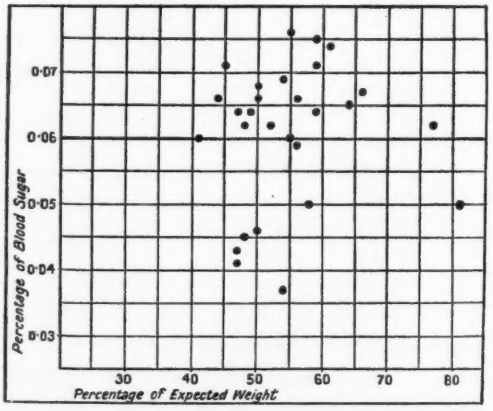
Blood-sugar compared with Weight Trends.

Gaining Weight.	Losing Weight.
0·041	0·037
0·043	0·057
0·045	0·059
0·050	0·062
0·050	0·064
0·060	0·064
0·062	0·068
0·064	0·072
0·065	0·074
0·066	
0·066	
0·066	
0·067	
0·069	
0·071	
0·071	
0·075	
0·076	
0·100	

The most striking fact observed in Table IV is that the blood-sugar determined three to four hours after food shows no relationship to the amount of carbohydrate ingested. Estimations were therefore made less than three hours after the ingestion of food. They are tabulated in Table VI.

CHART.

Atrophic Infants. Blood taken 3–4 Hours after Food.



Although the general level is higher after the shorter interval, there is no correlation between the amount of carbohydrate ingested and the amount observed in the blood-sugar. However, no conclusions can be drawn as to the adequacy of absorption without further observations, repeated at short intervals

during the absorptive period, upon both normal and marasmic infants receiving the same diet.

TABLE VI.

Atrophic Infants. Blood taken less than Three Hours after Food.

No.	Age.	Weight in Grm.	Percentage of Expected Weight.	Trend.	Calories per Kilo.	Calories per Expected Kilo.	Grm. of Carbohydrates per 24 Hours.	Blood-sugar, L.-B. Test.	Plasma Bicarbonate, Van Slyke Test.	Hours after Food.	Diagnosis and Result.		
26	9/52	2892	64	L	26	14	2·97	0·050	62·4	1	Marasmus.	V	Died
27	5/12	3968	62	S	117	73	50·87	0·050		1	Marasmus.	V	Well
14	6/12	4226	60	L	60	36	11·76	0·055	58·4†	1	'Intoxication.'	V	Died
24	10/12	5386	61	L	6·5	4	1·68	0·065	43·0	½	'Intoxication.'	V	Died
17	7/12	6126	81	L	112	93	11·76	0·066	57·4†	2	'Intoxication.'	V	Died
45	5/12	4226	66	L	32	20	5·95	0·066		1	Marasmus.		Well
29	6/12	2695	38	L	145	56	50·87	0·070	57·6	1	Marasmus.		Well
18	7/12	3632	48	G	108	52	30·24	0·071	51·6	1	Marasmus.		Well
40	2/12	2466	54	G	132	73	25·51	0·073		2	Marasmus.		Well
21	7/12	4052	54	S	63	34	11·76	0·077	66·2	1	Marasmus.		Well
16	5/12	3116	48	G	69	34	10·01	0·080	56·5	1	Marasmus.		Well
14	6/12	3912	35	L	117	65	31·87	0·083	45·3	2	'Intoxication.'		Died
19	5/12	3968	63	L	60	39	11·76	0·083	62·8	1	Marasmus.		Died
14	5/12	4114	64	L	31	19	5·88	0·089	69·0†	½	'Intoxication.'		Died
28	4/12	6468	111	L	Water only for 24 hrs.			0·090		16	'Intoxication.'		Died
41	3/12	4260	81	G	60	49	11·90	0·098		1	Convalescent pyloro-spasm		
46	10/12	4736	54	L	105	51	54·6	0·100		½	Marasmus.		Well
35	5/12	3430	53	L	35	17	5·21	0·100	42·9	2	'Intoxication.'		Died
39	11/12	4450	49	L	32	15	3·19	0·100	57·6	2	'Intoxication.'		Died
19	5/12	3716	53	L	118	62	64·49	0·100	61·4	¾	Marasmus.		Died
25	4/12	4596	79	L	7·6	6·2	1·68	0·100	37·5	¾	'Intoxication.'		Died
20	2/12	3178	70	L	38	27	5·6	0·142	38·1	1	'Intoxication.'		Died

V Indicates that the infant was vomiting during day on which blood was analysed.
† Patient was receiving sodium bicarbonate therapy.
G Gaining weight.
L Losing weight.
S Stationary.

In this series also, all the cases with distinctly low blood-sugars had been vomiting on the day of analysis.

Discussion and Conclusions.

As carbohydrate is absorbed it is probably largely stored by the liver and muscle and given off to the general circulation in amounts sufficient to keep the percentage of dextrose in the blood at the normal level. This is maintained until the sources of carbohydrate are entirely depleted, for even after prolonged starvation no change is observed in the percentage of blood-sugar. The assumption that the rise in blood-sugar observed in animals and adult man after the ingestion of a meal is due to the absorbed carbohydrate of that meal, supposes that a large excess of carbohydrate is thrown into the portal circulation, and that in its

passage through the liver glycogenesis is not able to store all of the excess, and that a certain amount, observable in the peripheral circulation, is passed on for immediate use or storage in the muscles and elsewhere. In the infant there are two factors which alter the conditions. In the first place, much of the food which is used in the adult for work and repair is used for growth, and it is probable that the storage mechanism is more active than in the adult. In the second place, regular and frequently repeated feedings are given, and although the carbohydrate is usually in the simple forms of lactose or saccharose, it is probable that absorption is almost continuous with, perhaps, a slight increase at a certain interval after the feed. Woodyatt, Sansum, and Wilder (6), in extensive investigations in animals and man, have demonstrated that 0·8 to 0·9 grm. of glucose per kilo body weight per hour can be utilized by the organism for an indefinite time without producing glycosuria. This fact was observed while using a slow steady systemic injection of glucose solution, and is called by them the 'utilization limit' of glucose.

A breast-fed infant of six months, weighing 7 kilos, probably does not get a litre of milk in twenty-four hours. However, in such a case the amount of sugar ingested would be 70 grm., i. e. (if the frequency of feedings and process of digestion and absorption permit the calculation) 0·4 grm. per kilo per hour—a figure considerably lower than the 'utilization limit' of Woodyatt. This relatively steady low entry of carbohydrate into the portal blood, with its subsequent passage through a young, active liver, may account for the lower general average of sugar in the systemic circulation of infants, as well as the rather steadier level relative to feedings.

Analysis of the data for the atrophic infant (Tables IV and VI) shows that the highest carbohydrate intake was 28·2 grm. per kilo per twenty-four hours, or 1·1 grm. per kilo per hour (No. 1). If all this carbohydrate was absorbed, a blood-sugar higher than 0·062 would have been expected, unless a very rapid storage is postulated. However, with this one exception, all cases show a carbohydrate intake of less than the 'utilization limit', although in most cases greater than that of the breast-fed infant. Therefore, if absorption goes on normally, there should be either an increase in blood-sugar or a rapid storing, or an increased excretion, or an increased oxidation. There is not an increase in blood-sugar; in fact, the general level is slightly lower than normal. The general condition of the infant suggests that sugar is not stored properly. He does not gain in weight. Undue excretion in the urine does not occur. The respiratory quotient as investigated by Fleming, as well as the subnormal temperature and general lack of muscular activity, do not suggest that sugar is oxidized extravagantly. Absorption is probably at fault.

No proof of this is found on examination of the peripheral blood. Since, among other possible influences, changes in blood-volume and immediate demands of muscular activity probably cause fluctuations in the percentage of sugar in the blood, such changes can hardly be assumed to be due to recently absorbed carbohydrate.

The only conclusions which may be drawn from these observations are:

1. In atrophic infants who are not vomiting, the percentage of blood-sugar, determined three to four hours after a feed, is slightly lower than the average normal.

2. In infants who are vomiting on the day of analysis, the blood-sugar is distinctly low.

3. Within the limits observed, there is no relationship between the amount of sugar ingested and the percentage of sugar in the blood, whether determinations are made three to four hours, or at a shorter interval after the feed.

4. There is no relationship between the percentage of sugar in the blood and the weight trend.

5. The percentage of sugar as usually observed in the peripheral blood cannot be used as an indication of carbohydrate absorption.

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NOTES ON FOUR CASES OF PAROXYSMAL TACHYCARDIA[1]

By E. E. LASLETT

THE purpose of this paper is to describe four cases of paroxysmal tachycardia, which are of different types and which show some special features of interest.

In the first three cases the paroxysms were apparently induced by excessive indulgence in tobacco. It has long been believed that tobacco may induce cardiac arrhythmia, but little has been written on the nature of the irregularity. Neuhof (3) describes a case of sino-auricular block due to tobacco poisoning, and also mentions that he has seen auricular flutter and fibrillation caused by the drug.

In two of the cases here described, there is very strong evidence that the paroxysms were caused by tobacco, because they ceased when smoking was given up, or much limited. In the third case, that of a young man who died suddenly at the end of an attack, there was no opportunity of testing the effect of abstention, but he had indulged very excessively in cigarettes for so early an age.

Case I. Paroxysmal Auricular Fibrillation.

W. M., cashier, aged 46, had been under treatment at the end of 1913 for dyspepsia. A tall, well-built, fresh-coloured man, he had been a heavy pipe smoker since boyhood. He confessed to 6 oz. of strong pipe-tobacco a week, with some cigarettes and a few cigars. For twelve to thirteen years he had been liable to attacks of palpitation, which sometimes persisted for twenty-four hours or more. The attacks were brought on particularly by sudden exertion. On December 20 I saw him in an attack. The pulse was quick and completely irregular, and a polygraph curve showed the ventricular form of venous pulse. The heart was not apparently enlarged and no murmurs could be heard. He was slightly cyanosed, but in no great distress, although he was rather breathless on moving about. He was evidently suffering from a paroxysm of auricular fibrillation. He continued at business, and two days later the tachycardia ceased. On the 23rd a polygraph curve showed sinus arrhythmia of slow rate, about 60 per minute, and unaccompanied by any extra-systoles. He gave up smoking for six months. A note in October, 1914, states that he now smokes 2 oz. a-week, feels much better, but avoids overwork and hurry. He has had no

[1] Undertaken on behalf of the Medical Research Council.

[Q. J. M., Oct., 1921.]

further attack. On March 13, 1918, during an air raid, he ran upstairs and immediately felt that his heart had 'gone wrong' again. This attack showed the same features as the last and continued for six days.

He remained well and free from paroxysms until May, 1921. He had been able to resume his ordinary activity, had not avoided hurry when necessary, and he seemed gradually to have got back to his former amount of smoking, although he used a milder mixture of tobacco. On the 15th, shortly after breakfast, while stooping in his garden, he felt unwell and, on rising to return to the house, fell in a faint on the grass. On recovery, he was conscious of palpitation, and a polygraph curve taken later showed the presence of auricular fibrillation with a ventricular rate of 190. Pressure on the right vagus readily produced long ventricular pauses (4 seconds). On the 18th he was given quinine gr. ii t.d.s., and on the 20th the normal rhythm had returned with no extra-systoles. Right vagus pressure now induced a pause of nearly four seconds, with no block and no alteration of the *a–c* interval at the end of the long pause.

There is no evidence of the nature of the attacks of palpitation which this patient had suffered for so many years before he came under treatment, but the fact that the first attack of which records were taken appeared to him to be of the same character as those he had had previously, is strongly suggestive that in the latter also the auricles were fibrillating. The paroxysms ceased entirely for nine months, for six of which he was a non-smoker; and then for seven years he had no further attack until the one observed this year. During the first half of this period the patient avoided over-exertion, but during the later years he has taken no special precaution in this respect, and he has gradually drifted back to his heavy smoking habit. Whether quinine had any influence in arresting the paroxysm or not, it is impossible to say.

Case II. Auricular Tachycardia.

T., aged 48, a short, stoutly-built man, of good personal and family history, consulted me on May 13, 1918, for attacks of giddiness from which he had suffered for about ten days. The attacks came on several times daily, and occasionally he seemed to lose consciousness for the moment, but he had never fallen down. For many years he had been a heavy smoker, his range being from fifteen to twenty pipes a day, and very occasionally a cigar. The radial arteries were somewhat tortuous and thickened, but easily pressed out. The heart was not enlarged, but there was a systolic murmur at the upper end of the sternum and towards the aortic area.

The pulse was extremely irregular. Long polygraph curves were taken (Figs. 2 and 3). These show that there was sinus arrhythmia, and that during each inspiration one or several successive auricular extra-systoles occurred, usually more than one. Towards the end of the curve it fortunately happened that two longer periods of tachycardia were caught, and during these he stated

that he had the peculiar feeling he complained of, and that if he had been standing he would have been very giddy. The irregularity was still present the next day, but though a long curve was taken no paroxysm of tachycardia was recorded. When he held his breath the irregularity almost disappeared (there were only two extra-systoles), to reappear with the first inspiration.

Tobacco was limited, and next day the pulse was only occasionally intermittent, and he had had no attacks of vertigo. A week later the pulse was regular at 64 per minute. He had limited his tobacco to a third of his previous amount, and there had been no further attacks. Two months later, during the temporary absence of his family, he smoked more freely for a short period, and he had a return of the 'dizzy attacks' for a few days; but when seen on two occasions during this period the pulse was found to be quite regular. He has remained well up to the present, and has, I believe, adhered to his moderate allowance of tobacco.

The disturbance in this case, as in the first, is one affecting primarily the auricular rhythm. The constant relationship of the extra-systoles to the period of inspiration, which persisted for two days, is a peculiar and unusual one. The two paroxysms of tachycardia also commenced during inspiration. Moreover, while breathing was suspended, the extra-systoles almost entirely ceased. It would seem that there was an irritable focus in the auricular muscle, the result it is suggested of tobacco poisoning, which was aroused in some way to greater activity by one of the incidents associated with inspiration. Whether it was a mechanical stimulus, the greater influx of blood to the auricle, or, as Dr. Lewis has suggested to me, a nervous influence 'just tipping the balance', cannot at present be determined.

Case III. Ventricular Tachycardia (?).

H. N., stoker, aged 19, was admitted to the Royal Naval Hospital, Hull, on April 25, 1917, with the history that he had fainted in the forecastle on April 19, and that on recovery the pulse was found to be intermittent and irregular. Four days later he had an attack of heart failure during which the pulse was uncountable. There was a history of scarlet fever and former heart affection, and he had been an extremely heavy cigarette smoker.

On admission the patient appeared comfortable and not obviously ill. There was no apparent enlargement of the heart, the sounds were normal and the rate slow and slightly irregular. While in the hospital he had three long attacks of tachycardia, during one of which long polygraph curves were taken of the pulsation in the neck and the apex beat. Owing to the feebleness of the pulsations it was found impossible to get a record of either brachial or radial pulses. The heart-rate, calculated from the curve, was found to vary slightly about an average of 240 per minute. Unfortunately, neither the onset nor the offset of the paroxysm was observed, and it is impossible to determine the focus of origin

of the tachycardia. The only evidence available is derived from the frequent extra-systoles which interrupted the normal sinus rhythm. These arose from a focus situated probably in the ventricles, but possibly in the junctional tissues. They were certainly not auricular. Now it is well known that, after the cessation of paroxysms of tachycardia, the normal slow rhythm is frequently disturbed by extra-systoles, and that usually these arise from the same focus as the beats of the paroxysm. It is probable, therefore, that the paroxysm did not proceed from the auricle, but either from the ventricle or *a.-v.* node. The rate of the heart during the attacks was unaffected by the firmest pressure on either carotid sheath.

During the attacks observed in the hospital the patient was very collapsed, pale, with a slight grey cyanosis. He was rather restless, but there was no respiratory distress. Just after the end of the third paroxysm, as he was still collapsed, he was given a hypodermic injection of pituitrin. He was able to talk to the ward sister, but it seems that when she returned after a momentary absence he was found to be dead.

This patient is said to have smoked as many as forty cigarettes during a four-hours' watch. This is doubtless an exaggeration, but it was agreed that he smoked to great excess at so early an age. He appears to have been able to do his work well before the onset of the syncopal attacks, and it is possible that there were latent myocardial defects, the result of scarlet fever in childhood, which were exaggerated by tobacco poisoning. Apparently death was due to exhaustion, consequent on the prolonged paroxysm of tachycardia at such a high rate. The mode of death is suggestive of ventricular fibrillation.

Case IV. Ventricular Tachycardia.

T., aged 55, railway guard, was first under my care at the age of 40, for a prolonged attack of rheumatic fever, from which he had also suffered at the age of 15. No valvular lesion could be detected after the illness. He was a short, stout man, with an emphysematous chest, and he had had frequent attacks of bronchitis in his later years. He had been frequently under treatment for this and attacks of rheumatism, but he had shown remarkable power of rallying, and this, combined with a strong disinclination to be off work, had often kept him going when other men would have been on the sick list. Since 1918 he had several times had oedema of the feet and once slight ascites. At the time of writing, owing to shortness of breath, he was able to keep at work only because it was very light signalling. Lately he had lost a good deal of flesh, and he was less troubled with severe bronchitis than formerly.

In December, 1919, he had a paroxysm of tachycardia which continued for two days, and thereafter for several days he had numerous shorter attacks. During the paroxysms, he preferred to sit, although he was able to lie down with comparatively little distress. Pressure over either carotid sheath was repeatedly

tried without any effect on the heart-rate. When the shorter paroxysms had ceased, the pulse continued irregular, owing to the frequent occurrence of single and multiple successive extra-systoles.

At the time of writing he suffers from rheumatism in the small joints of the feet. The cardiac dullness is diminished and the apex beat obscured. No murmur can be heard. The rhythm is intermittent.

While paroxysmal tachycardia of auricular origin is not uncommon, the ventricular form is rare. Robinson and Herrmann (4), in a recent paper, state that in their opinion only six undoubted and six probable cases have been recorded. They consider only those cases based on electro-cardiographic evidence. They add four cases of their own. Gallavardin (1), not mentioned in their review, describes one case in which the auricular rhythm remained unchanged during the access of tachycardia, although the rate of the auricles, slightly variable, was at times exactly half that of the ventricles.

Lewis (2) points out the great difficulty of demonstrating the ventricular origin of tachycardia, even with the aid of an electro-cardiogram, unless the first or last beat of the paroxysm is recorded. It would, therefore, seem to be presumptuous to publish a case on the evidence of the polygraph alone, but it fortunately happened that either the onset or the offset or both of a number of short paroxysms were recorded, and these curves show uniformly the same features, which, as it seems, prove that the tachycardial attacks cannot have been other than ventricular in origin. It may here be mentioned that for the past seven years this patient has had almost constantly an intermittent pulse, and curves taken occasionally at the earlier part of this period, and more frequently in the last two years, have always shown that the intermissions were due to ventricular extra-systoles, although, owing to the difficulty of recording the venous pulse, the proof of this often depended on the fact that the compensatory pause was of full length. Recently many venous curves have been taken, and they all show numerous extra-systoles ventricular in origin.

The onset of a paroxysm is shown in Figs. 4 and 5. The average rate is 210 per minute, and the radial pulse is alternating. The smaller beats are at times difficult to distinguish. They are best seen in Fig. 6. In Fig. 4 the auricular wave, which occurs during the apparent pause before the onset of the tachycardia, obviously belongs to the normal rhythm as it occurs at the expected time, and the considerable interval which separates the wave from the first beat of the paroxysm shows that the latter is not a response to the auricular impulse. The next auricular wave, marked a', appears after a shorter interval, and is followed by waves at the same shortened intervals and corresponding to alternate radial beats. In Fig. 5 there are at the beginning of the paroxysm apparently two auricular waves of the slow rhythm. The second wave is judged to belong to the normal rhythm because it occurs after the same pause, and also at a greater interval after the first beat of the paroxysm than a' does after the third.

At the offset of a paroxysm (Fig. 6) the last auricular wave marked a' is

judged to belong to the paroxysmal rhythm because it occurs after the same interval as separates the preceding waves, and at a slightly increased interval before the first auricular wave of the slow rhythm.

It is suggested that the paroxysms are due to an independent ventricular rhythm, and that, at a variable but short interval after the onset of the tachycardia, the auricles respond to retrograde impulses from the ventricles, but at half the rate, alternate impulses being blocked.

Put briefly, this interpretation is based on the following reasons:

(1) The first beat of the paroxysm occurs independently of the auricle.

(2) The auricular rate during the paroxysm is half that of the ventricle, and is greater than the auricular rate of the slow rhythm.

(3) The increase of the auricular rate is sudden, and appears after the first few cycles of the paroxysm.

At a later date a long paroxysm at a lower rate (173) was recorded (Fig. 7). Alternation is not present in this curve, doubtless because of the lower frequency. At first sight this has the appearance of auricular tachycardia, but every few cycles the auricular wave is wanting. This is not the effect of respiratory movement on the vein, because the auricular pauses bear no relation to the respiratory dip in the curve, and also because they were present as frequently during suspended respiration. The suggestion is made that it is in reality a ventricular tachycardia in which, owing to the lower rate, the bundle is able to conduct for the most part successive retrograde stimuli, though it fails every now and then to do so, and the auricle does not then contract. The termination of this paroxysm was recorded, but the curve is too defective to reproduce. It shows, however, clearly that the last auricular wave of the paroxysm occurs *after* the last radial beat and the slow rhythm commences after a long pause.

Not improbably the focus of origin of this paroxysm was at a different level, perhaps higher than that of the earlier paroxysms. The remainder of the curve in which this paroxysm was recorded showed numerous single and two successive ventricular extra-systoles.

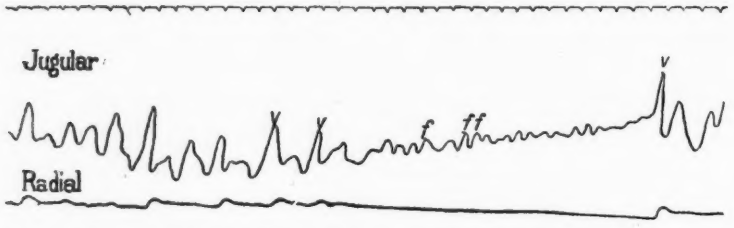

FIG. 1, Case I. Ventricular venous pulse. A pause of 4 secs. induced by pressure on right carotid. The *f* waves are prominent during the long diastole.

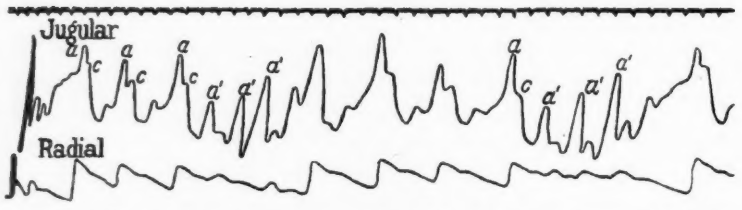

FIG. 2, Case II. To show the occurrence of multiple auricular extra-systoles during inspiration (where the venous curve dips).

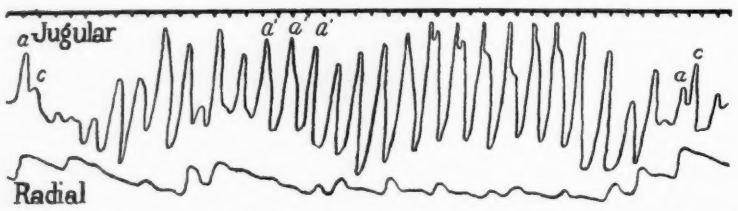

FIG. 3, Case II. To show a short paroxysm of auricular tachycardia, which commences during inspiration. There is a fall of blood-pressure, as shown by the general fall of the radial curve, and many of the beats are abortive. Rate 192 per min.

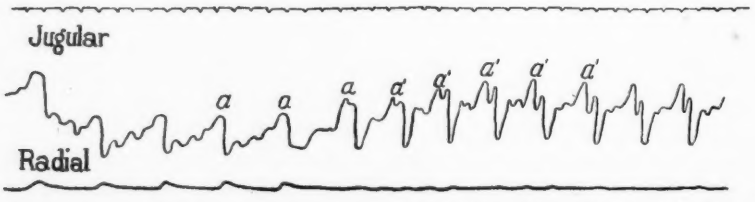

FIG. 4, Case IV. The onset of a paroxysm of ventricular tachycardia. In this figure and the next it is possible that there is an abortive ventricular beat during the pause after the last beat of the slow rhythm. Rate of the paroxysm 211 per min.

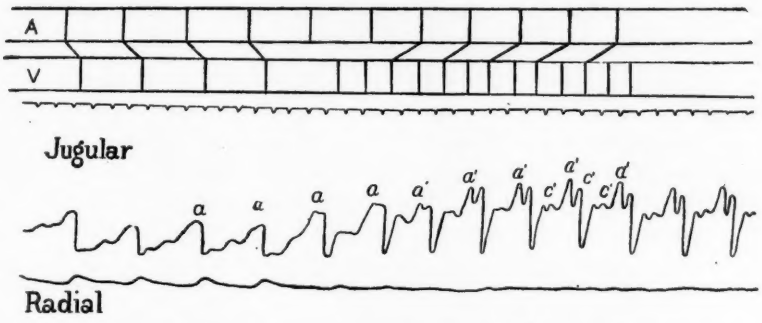

FIG. 5, Case IV. To show the same as the previous figure, except that there are two normal auricular beats before the auricle begins to respond to alternate retrograde stimuli from the ventricle. The diagram above the curves shows the suggested mechanism.

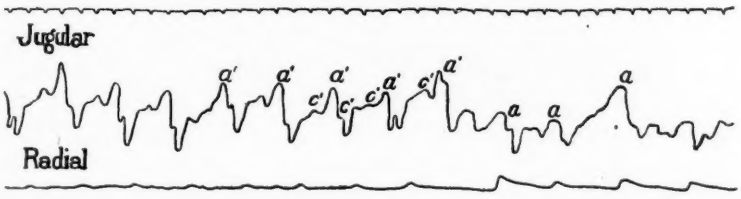

FIG. 6, Case IV. To show the offset of a paroxysm. There is a short pause between the last auricular wave (*a'*) of the paroxysm and the first auricular wave (*a*) of the slow rhythm.

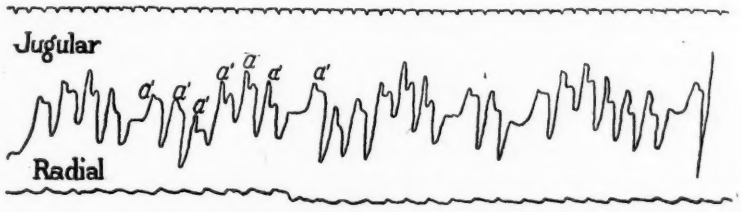

FIG. 7, Case IV. To show the paroxysm at a lower rate. The tall peaks marked *a'* are believed to represent auricular waves. At six places these are absent owing, it is suggested, to failure of conduction of the retrograde stimulus from the preceding beat. The radial pulse is not alternating. Rate 173 per min.

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AN INQUIRY INTO THE CLINICAL MANIFESTATIONS OF A SYPHILITIC INFECTION UPON THE HEART[1]

By WILLIAM STOBIE

1. *Introduction.*

It is generally accepted that the most frequent cause of aortitis and of aneurysm of the aorta is syphilis, and these conditions are usually treated by anti-syphilitic measures. With diseases of the heart itself, there is often no such certainty as to the aetiological factor in a given case. Apart from the acute types of endocarditis due to the streptococcus, gonococcus, &c., and the disorders of the heart following influenza, trench fever, diphtheria, and other acute illnesses, the largest share by far in the causation of heart disease is agreed to be held by acute rheumatism. Next to rheumatism come chorea, tonsillitis, and scarlet fever. In 101 cases of heart disease, Lewis (1) found a previous history of rheumatic fever or chorea in 61 per cent., and of tonsillitis in 6 per cent.

Frequently, however, cases are seen in which no rheumatic history can be obtained, and yet where an undoubted infection is, or has been, present. The object of this inquiry has been to ascertain, by all methods available, the proportion in which injury to the heart by syphilis occurs in clinical practice.

The subject has been investigated from various standpoints. Through the courtesy of the honorary staff of the Radcliffe Infirmary and County Hospital, Oxford, I have been enabled to look up the records of autopsies on cases of heart disease over a period of years, and to correlate the clinical and post-mortem findings. Material has been obtained from the Pathological, Out-patient, and Venereal Departments, as well as from the wards of the hospital; from the Oxford Eye Hospital, homes for mental defectives, workhouse infirmaries, and private sources. The Pensions Medical Board at Oxford has also furnished cases. A close inquiry into the personal and family history of patients with evidence of 'morbus cordis' has been made, and special attention has been paid to the condition of the heart in persons suffering from syphilis in the various stages and in those where a previous history of syphilis has been acknowledged or recorded. In certain instances, signs suggestive of the disease, or a suspicious family history, have, by themselves, led to the examination of the heart.

[1] Accepted as a thesis for the degree of M.D. in the University of Edinburgh.

[Q. J. M., Oct., 1921.]

2. *Historical.*

In *A System of Syphilis*, Osler and Gibson (2) state that syphilis of the heart was mentioned in the literature as far back as 1736. French writers appear to have paid particular attention to the condition, and the names of Laennec, Bouillard, and Corvisart are frequently met with in descriptions of cases. Lancereaux (3) mentions a case which was quoted in 1775 in the *Mémoires de la Société royale de Médecine*, of a young woman aged 22, who during life had marked signs of syphilis, and who had cardiac symptoms and acute pain in the region of the heart before death. At the post-mortem nearly the whole of the posterior surface of the heart was found to be occupied by a large ulcer which had only a few muscular fibres in a thin layer as a base. The same writer describes two cases where the wall of the left ventricle was very sensibly thickened, and presented on section a smooth, shining, lardaceous-looking surface of a yellowish-grey colour and of a slightly unctuous consistence.

In Ricord's (4) *Atlas*, published in 1851, is an illustration of the heart from a man aged 41, who died suddenly, and who had a history of having contracted a chancre when 20 years of age, another at 30, and possibly a third between these dates. In this specimen gummata in various stages are seen in the walls of both ventricles.

In 1862 Haldane (5) recorded the case of a young woman, 25 years of age, who died suddenly in a brothel in the High Street of Edinburgh. The heart showed on the anterior surface of the left ventricle near the septum a flattened mass $\frac{1}{4}$ inch long by $\frac{1}{8}$ inch broad, slightly projecting, and when cut into, moderately firm and of a pinkish-grey colour and extending $\frac{1}{8}$ inch into the muscular substance.

In 1863 Wilks (6) recorded the case of a man aged 29, who died suddenly without any previous illness, but who had been subject to fainting attacks since childhood. He was a hard-working man, who suffered occasionally from severe momentary attacks of pain in the left side of the chest. At the autopsy the muscular wall of the right ventricle was found to be replaced by a solid tough mass of fibrous tissue extending from the mid ventricle upwards into the pulmonary artery, and of greatest thickness at the base of the heart. This was regarded as probably of congenital origin.

In 1874 Fagge (7) recorded eleven cases of fibroid disease of the heart-wall met with in one year in the post-mortem room of Guy's Hospital. One of the cases was that of a woman aged 30, with extensive fibroid disease of the left ventricle and multiple aneurysms, while another was that of a man of 43 years, with extreme fibroid disease of the left ventricle extending into the septum, and causing aneurysmal yielding of the walls.

Ten years later Hale-White (8) extended Fagge's series by recording another nine cases of fibroid disease of the heart causing sudden death, and laid stress on the frequently unexpected nature of the sudden death. Four patients out of the nine bore evidence of syphilis in other parts of the body.

In 1875 Pearce Gould (9) read before the Pathological Society of London a paper on the case of a man aged 40, who had died suddenly, and the anterior wall of whose right ventricle was composed of a grey-white material extending into the auricle. The condition was thought to be a carcinoma, but on microscopical examination was demonstrated to be a gumma.

In 1878 Grenouiller (10) wrote a Paris thesis on cardiac syphilis, collecting twenty-four instances from various sources. He concluded that syphilitic myocarditis began as a small gumma and ended as a patch of sclerosis. He stated that the average date of onset after infection was ten years, although one case began during the first year. He considered that there were no special symptoms, though heart disease was frequently suspected, and he found that two-thirds of the cases terminated in sudden death.

Lang (11) in 1889 gave a complete bibliography to date, and published a table showing that over 84 per cent. of cases of syphilis of the heart occur between the ages of 28 and 37 years.

Mauriac (12), in an exhaustive article, quotes as an example the case of a man aged 25, who had been infected with syphilis five years previously, and who came under observation when suffering from violent headaches (most severe at night), ulceration of the scalp, a slight cardiac hypertrophy, and an aortic diastolic murmur. There was no history of rheumatism, and there had been no cardiac symptoms until he began to have palpitation and tachycardia a few months before being seen. The patient quickly responded to large doses of iodide of potassium, and in five months there was no trace of the gummata of the scalp, the heart appeared to be functioning naturally, and no bruit could be detected.

In 1897 Phillips (13) collected twenty-five fatal cases of syphilitic disease of the heart-wall, and described in detail the lesions found at the post-mortem examination. In twenty of these cases sudden death occurred.

Sir Jonathan Hutchinson (14) quoted cases that have been recorded from time to time in this country, and includes one reported in 1875 by Dr. Cayley where, in the wall of the left ventricle, several roundish nodules of a whitish colour were found. This specimen came from a young man of 28 years of age, who was known to have had syphilis several years before. The same writer states that Mr. Shattock, in 1880, showed at the Pathological Society the heart of an infant, where there was present in the right ventricle a gumma involving the under side of the cusp of the pulmonary valve.

There are also recorded the cases described by Rolleston in 1893, where there were a number of white nodules in the wall of the right ventricle; a gummatous condition of the left testicle was also noted.

From the London Hospital in 1906 two similar cases with gummata in the testicles are also mentioned by Hutchinson.

Several cases of congenital syphilis, in which the heart has been found to be affected, are also recorded.

Fournier (15 and 16) has noticed in subjects of inherited disease: one instance of absence of the right heart; four instances of persistence of the ductus

arteriosus; five instances of patent foramen ovale; nine instances of congenital cyanosis; two instances of the narrowing of the pulmonary artery and aorta; one instance of the narrowing of the mitral valve; one instance of aortic insufficiency; and, incidentally, he states that Raynaud's disease has been noted in cases of two newly-born children suffering from hereditary syphilis.

This writer maintains that mitral stenosis is often the result of transmitted syphilis, being found not uncommonly in descendants of syphilitic parents, and he brings forward many instances to support this claim. He also mentions two cases of pulmonary stenosis which he believed to be of hereditary syphilitic origin.

Anderson (17) records a case of rupture of the ventricular wall in a five-year-old child, resulting from myocarditis following inherited specific disease, and where spirochaetes were found in the heart-muscle.

Warthin (18) holds the view that congenital disease of the heart is comparatively common, but the condition has to be looked for with the microscope. He believes it is a common cause of sudden death in infancy. Gummata, he states, are rare, and the lesions he describes occur in the form of areas of epithelioid proliferation along the course of the smallest vessels, and apparently arise from the walls or from the perivascular tissue. The muscle fibres in the neighbourhood undergo a necrosis. Spirochaetes can be found in large numbers.

Neugebauer (19) described three cases in the same family where there were symptoms of shortness of breath, precordial pain, and palpitation, and where on examination he found an enlarged heart and a double aortic murmur. The ages of the patients were respectively—21 (female), 28 (male), and 17 (female). Their mother had had three previous miscarriages, and in all the above cases the Wassermann reaction was positive, and there was no history of rheumatic fever. The same writer records a case of a girl, aged 18 years, with similar symptoms, with a positive Wassermann test but no antecedent illness. There was in this patient also a double aortic murmur, and the X-rays showed an enlargement of the ascending aorta extending to the beginning of the arch.

On the other hand, Findlay (20) is inclined to regard as rare aortic disease due to congenital syphilis, but he cites the case of a boy, aged 15, with symptoms of precordial pain and breathlessness, with a double aortic murmur, cardiac enlargement, and a Corrigan's pulse. The patient had well-marked features of inherited lues, a positive Wassermann reaction, and no personal or family history of rheumatism.

De Stefano (21), in examining a series of congenital anomalies and malformations at the Naples University Paediatric Clinic, found the Wassermann reaction positive in 27 patients out of a total of 32 cases of congenital heart disease.

3. *Pathology.*

All three layers of the heart may be affected by syphilitic changes.

Pericardium. The pericardium is rarely involved in itself. As McPhedran (22) says in Osler and McCrae's *System*, the subject is one of academic rather than one of practical medicine. In Phillips's (13) series of 25 cases the pericardium was involved in five. Gummata of the pericardium are very rare.

Lancereaux (3), while admitting the rarity of the condition, accepted the possibility of a syphilitic infection of the pericardium either as fibrous bands between the visceral and parietal layers, or as small scattered gummata. Some writers consider that some of the 'milk spots' may be of specific origin.

Oddo and Mattei (23) have recently described a case of syphilitic pericarditis in a man aged 25 years. The patient was admitted to hospital with well-marked signs of secondary disease, and gave a history of 15 days' dyspnoea, worse for eight days previous to admission. Clinical features of pericarditis were present, together with marked cyanosis, swelling of the veins of the neck, and oedema of the legs. The Wassermann reaction was strongly positive. Under intravenous injections of mercury the patient improved for a time, and then relapsed. He rallied with novarsenobenzol, but after the fourth administration collapsed from generalized pulmonary oedema.

At the autopsy numerous dull villous patches were found on both layers of the pericardium, and on microscopical examination these showed the typical appearances of a syphilitic lesion. The myocardium and endocardium were normal.

Myocardium. The myocardium may exhibit either gummatous growths varying in size and situation, or areas of diffuse fibrosis which replace the muscular tissue partly by narrowing of the vessels from endarteritis obliterans, and partly by pressure of the proliferating connective tissue cells. Weakness of the muscle results, and aneurysmal dilatations may occur. Examples of such lesions are to be found in most hospital museums. In such cases the heart-muscle is seen under the microscope to be replaced by a small cell infiltration with many fibrous tissue cells. The arteries appear thickened, especially in the media and adventitia.

Endocardium. In the endocardium a common site of deposit is on the septal wall, but it may occur elsewhere, and the disease then presents itself in the form of small localized thickenings, or as larger plate-like masses which often send fibrous processes into the myocardium.

Inflammation of the valves, due primarily to syphilis, has generally been considered as rare. As an acute infection the *Spirochaeta pallida* is, according to Dreschfeld and McCrae (24), very rarely, if ever, the cause. Indirectly, syphilis was regarded as a possible cause of chronic endocarditis, acting through a general arterio-sclerosis. The aortic valves may be, and frequently are, affected by a spread of the inflammatory process from the aorta.

Longcope (25) considers that in 34 per cent. of cases of aortitis the valves are also affected, and Symmers and Wallace (26) place the figure at 27 per cent. where aortitis is found associated with sclerosis and retraction of the aortic valves.

Turnbull (27) finds evidence of aortitis in over 60 per cent. of post-mortems in cases of acquired syphilis. In over 15 per cent. there was endocarditis of the aortic valves, which he attributes directly to syphilis. In just over 1 per cent. myocarditis was present.

Hutchinson (14) quotes instances of what have been termed condylomata of the valves of the heart and he accepts their syphilitic origin.

Moore (28) reports the case of a woman, 31 years of age, with mitral stenosis and aortic valvular disease, who had sores in the mouth and a positive Wassermann reaction, and also that of a man, aged 38, who had a condition diagnosed by several physicians as pulmonary stenosis, with commencing aortitis, both apparently of recent origin. The Wassermann reaction was strongly positive, and the man's wife had been pregnant once and had aborted.

Aortitis is closely associated with syphilitic disease of the heart. Turnbull (27) fails to find evidence that syphilis induces atheroma, but he believes that syphilitic inflammation of arteries is liable to lead to fatty degeneration and calcification. He has not found this inflammation to be confined to the intima of a large elastic artery as is the case in atheroma. In the early stages there is a moderate degree of perivascular inflammation of the adventitia, extending into the media by way of the capillaries, which are increased, and which spread into the intima. Muscular and elastic tissues begin to lose their structure due to pressure and swelling; in a later stage some atheromatous changes in the form of fatty degeneration and calcification occur.

The syphilitic inflammation in the early stages can be distinguished from the atheromatous change by the so-called rubbery consistence, the pearly colour, the longitudinal ridging and furrowing, and localized puckering, and the presence of spirochaetes in these areas.

In another article elsewhere, Turnbull (29) records two cases of aortitis in patients suffering from congenital syphilis, and gives the post-mortem findings. One case was that of a girl, aged 17, whose father had died some time previously. At the autopsy he was found to have aortitis with involvement of the aortic valves. This girl herself suffered from shortness of breath and presented signs of a double murmur at the aortic area and an occasional presystolic murmur at the apex of the heart. She died suddenly, and at the post-mortem the left ventricle was very much hypertrophied and dilated, and the heart weighed 1 lb. There was a crenated and pitted zone in the first inch of the aorta. In another case, that of a girl aged 7, the intima in the ascending and descending aorta was wrinkled and showed nodular thickenings.

The coronary arteries may be affected by an endarteritis giving rise to a myocarditis in the area of the distribution of the vessels.

4. *Symptoms.*

While there are no pathognomonic symptoms associated with syphilitic disease of the heart, there are certain features which are suggestive and which, if recognized, may lead to the relief of the patient's condition under appropriate treatment.

Symptoms depend largely on the site of the lesion. If the disease is limited to deposits of small size, and which are scattered in the heart-wall, no disturbance of function may be detected, but these foci are always a potential source of cardiac weakness and failure. If of large size, and especially if near the apex of the heart, sudden death is liable to occur. This has been noted by many writers, and may occur very early in the course of the disease, as in a case reported by Brooks (30), where before the rash had fully appeared death took place suddenly, and a minute perforation of the wall of the aorta just above the ring was found.

If the coronary arteries are involved in the inflammatory process there may be anginal attacks. These, if in a young man, and if of the true type and associated with referred pain or tenderness, should raise the suspicion of an infection by the *Spirochaeta pallida*. So also should attacks of arrhythmia and tachycardia without obvious cause.

The Stokes-Adams syndrome may be the manifestation of a gummatous infiltration of the bundle of His, as in the case reported by Handford (31). The patient died in one of the attacks, and at the post-mortem examination there were found numerous gummata in the myocardium, especially in the neighbourhood of the auriculo-ventricular groove. The mitral valves were slightly incompetent and the valve curtains were a little thickened.

A remarkable case of involvement of the auriculo-ventricular bundle has been fully detailed by Keith and Miller (32).

A man with a history of a sore on the penis 20 years previously came under observation for palpitation and syncopal attacks with loss of consciousness for a few seconds. Under treatment by iodides these symptoms gradually passed off, and until his death 12 years later from peritonitis following a perforation of the appendix, the patient had a pulse of about 42 beats per minute, and great dilatation of the veins of the right side of the abdominal wall.

When the heart was examined at the post-mortem, the superior vena cava was found to be completely destroyed, as also was the commencement and the upper half of the main auriculo-ventricular bundle. And yet at the time of the man's last illness there were no signs of heart failure, and it was thought that the recovery from the initial syncopal attacks was probably due to the remaining part of the auriculo-ventricular bundle taking on an automatic power of originating ventricular contraction.

Other symptoms of organic heart disease, such as shortness of breath on exertion, dyspnoea, and palpitation, may of course be present.

A special variety of cardiac asthma is mentioned by Stockman (33) as having been regarded as suggestive of heart syphilis. In a collection of 76 cases of gummata of the heart-wall, to which he himself adds four, he mentions tachycardia, arrhythmia, and dyspnoea as the predominant symptoms, and in only three out of the 80 cases were there signs which might be regarded as anginal.

Luce (34) considers that syphilis of the heart may be diagnosed (all other aetiological factors having been excluded) if heart symptoms suddenly or gradually appear without any obvious clinical cause in young subjects with a positive blood Wassermann reaction. The localization of syphilis in the septum may sometimes be established clinically by the appearance of valvular rupture, either spontaneous or following trauma, when a gummatous nodule in the region of the septum has broken through and opened communication between the right and left heart.

With or without slight cardiac enlargement and an occasional apical systolic murmur there may occur extra-systoles; these and other slight irregularities of rhythm in a heart suspected of disease should never be dismissed as of no importance.

Extra-systoles are frequently present in rheumatic affections of the heart, and according to Mackenzie (35) result from an increased excitability in the neighbourhood of the primitive cardiac tube. As this is a common site of syphilitic infection of the heart, it is suggested that extra-systoles in patients with evidence of specific disease may be an early manifestation of cardiac involvement. There is a tendency at the present time not to attach much importance to premature contractions, and many writers, Osler and Mackenzie included, have cited instances of patients with these 'carrying on' for years. The attitude of Lewis (36), regarding premature contractions as consisting of and bearing witness to defects, though they may be present constantly and for long periods without any other signs of cardiac disability, appears sound. Out of 121 cases of premature auricular and ventricular contractions as many as 86 were judged by Lewis to have a purely cardiac basis.

Symptoms such as have been described—angina, precordial pain, dyspnoea, and syncopal attacks with arrhythmia, tachycardia, and extra-systoles—may occur early in the disease and may be associated with a slight rise of temperature. Manifestations of heart-block and the Stokes-Adams syndrome occur in the later stages and indicate gross changes.

Although there are no distinctive signs of syphilitic infection of the heart, it is well, when a patient presents himself with cardiac symptoms and signs without any history of the more usual infections, to suspect syphilis as a cause, as Chapman (37) insists, and to seek diligently for confirmatory evidence.

ORIGINAL OBSERVATIONS.

Series 1. *Evidence of Cardiac Syphilis at Autopsy.* 5 Cases.

Case I. Gumma of endocardium.

H. H. In the Pathological Museum at Oxford is a specimen of a heart which came from a man aged 37, an old soldier, with no definite history of syphilis, although the risk of infection was not denied.

While the patient was in hospital the heart was noted as being enlarged to the left: there was a soft systolic murmur at the apex, and the heart occasionally had a gallop rhythm. The impulse was forcible, but the sounds feeble.

The patient died suddenly, and at the post-mortem examination the heart was found to be enlarged in all its cavities, least marked in the left auricle: the tricuspid orifice admitted four fingers and the mitral three, but there was no endocarditis of the valves.

In the right auricle there was an old thickening, 1 cm. broad, just below the entrance of the superior vena cava. In the left ventricle on the septal wall, 2 cm. below the interval between the right and left anterior cusps of the aorta, was a raised yellow area, irregular in outline, about 2 cm. broad, covered by endocardium, which elsewhere was thickened. The lesion interrupted an anterior branch of the bundle of His going to the anterior wall of the left ventricle. The endocardium covering the anterior wall was thickened and yellow, but was not raised.

Case II. Fibrosis of myocardium found in a patient with marked signs of tertiary syphilis.

J. W., a man aged 40, was admitted to hospital for an accidental gunshot wound and died on the following day. He was well nourished, had a sunken bridge of the nose, a recent gumma with a necrotic centre in the right calf, and two gummata in the right tibia, which was thickened and curved. The posterior part of the palate on the left side was eaten away by an old gumma, the cicatrix of which was visible. The heart was enlarged, with an excess of fat in the epicardium. The muscle was pale, with many fibrous trabeculae running in from the surface. There was some old perihepatitis, and both testicles showed areas of fibrosis. Unfortunately it is not known whether this patient suffered from any symptoms or signs of cardiac disorder.

Case III. Aneurysmal dilatation of heart-wall: recent endocarditis.

F. P., aged 31 years. Patient was a man who gave a history of, eight weeks before admission to hospital, having felt weak in the legs, especially the left, in getting out of bed in the morning. After breakfast he fell down. His wife stated that the left arm suddenly became weak and tremulous five months before admission. (? Embolus.)

On admission to hospital the patient was tremulous in his speech, but coherent. He had two ulcers on the sole of the right foot which were looked upon as 'perforating'. The Wassermann test was positive and there was considerable cardiac enlargement, with a soft systolic murmur at the apex and a loud diastolic bruit in the aortic region conducted down the sternum. The temperature ranged between 102°–105° F. for eight days and the diagnosis of malignant endocarditis was made.

At the autopsy the heart was found to be enlarged, the aortic valve was almost entirely obliterated by masses of irregular clot, and the orifice of the aorta much encroached upon. Extending to the right was an aneurysmal dilatation, which was just beginning to break through into the right auricle above the attachment of the anterior part of the septal cusp.

Case IV. Thickenings of endocardium: changes in coronary artery.

In the following case the clinical signs and appearances found in the heart of a young man strongly suggest syphilitic infection.

D. W., aged 35, was admitted to hospital with a recent history of shortness of breath and precordial pain. There was no history of acute rheumatism. There are no records of a Wassermann test having been made, or of any infection by the *Spirochaete pallida*. With slight cardiac enlargement, the contractions were noted as being rapid, but only one in every three or five reached the wrist. With the first mitral sound was a faint systolic murmur.

The patient died suddenly, and at the post-mortem there were found in the septum of the left ventricle four patches of old endocarditis each 0·5 cm. across. There was some 'atheroma' of the anterior branch of the left coronary artery, and in the liver were two small calcified nodules and a patch of perihepatitis.

Case V. The heart in congenital syphilis.

Female child, five weeks old, admitted to hospital for drowsiness, and because she would not take the breast. The child presented signs of syphilitic infection of the hands and feet (pemphigus), and only survived two days.

At the post-mortem examination there was found an increased amount of pericardial fluid in which spirochaetes were demonstrated. There was thickening and opacity of the pericardium and an extreme degree of pallor of the heart-muscle. Beneath the pericardium and in the myocardium were petechial haemorrhages and a small miliary gumma was visible under the endocardium. The liver also showed miliary gummata, and the characteristic changes were seen in the epiphyses.

Series 2. *Cases with Signs of Cardiac Lesions.*

1. *Aortic Disease.*

Case I. Aortic incompetence. A man, R. H., aged 46, who complained of occasional angina-like attacks and tenderness of the left biceps. He presented signs of slight cardiac enlargement. At the apex of the heart there was an impure first sound, and a rough systolic bruit at the aortic base with an occasional regurgitant murmur. There was a history of an obscure lesion of the central nervous system when the patient was 40 years old, the exact diagnosis of which does not appear to have been made. He had had several attacks of unconsciousness while he was at work, and a transient paralysis of the lower limbs. No history of syphilis could be obtained, but the Wassermann reaction was positive, and it is probable that the old attacks were of a specific nature. There were no abnormal signs in the central nervous system at the present date.

Case II. Aortic incompetence. J. B., male, aged 47, old soldier, admitted to hospital for shortness of breath, oedema of legs, and ascites. Good colour, double aortic murmur, double pleural effusion, enlarged hard spleen, slight hepatic enlargement. History of syphilis in India in 1895. Wassermann reaction + + + +. Much improvement with mercury and iodides.

Case III. Aortic incompetence. E. M., male, aged 38, old soldier. Visible pulsation in carotids, brachials, &c. Double aortic murmur. X-rays show dilated, very pulsatile aorta. No history of syphilis. Served in India, S. Africa, and Malta before the war of 1914–18. Had enteric fever in S. Africa. Wassermann reaction + +.

Case IV. Aortic incompetence. A. E. W., male, aged 21. Slight enlargement of heart. Double murmur over aortic area. No history of rheumatic fever or syphilis. Wassermann reaction + +.

Case V. Aortic incompetence. C. E. H., male, aged 36. Considerable cardiac enlargement. Apex beat in sixth space in mid-clavicular line. Systolic murmur at apex. Double murmur at aortic base with thrill. No history of rheumatic fever or syphilis. Wassermann reaction + + +.

Case VI. Aortic incompetence. C. A., male, aged 35. Considerable enlargement of the heart. Apex beat in sixth space, one inch outside mid-clavicular line. Impulse diffuse and heaving. Double murmur in aortic area with a thrill. History of gonorrhoea when 19. Wassermann reaction + + + +.

Case VII. Aortic incompetence. A. E., male, aged 39. Cardiac enlargement. Apex beat in fifth space in mid-clavicular line, heaving in character. Double aortic murmur with an Austin Flint's murmur at the apex. No history of rheumatic fever or syphilis. Wassermann reaction + + + +.

Case VIII. Aortic incompetence. T. H., male, aged 43. Slight cardiac enlargement. Double aortic murmur. No history of syphilis. Wassermann reaction + + + +.

Case IX. Aortic stenosis. R. S., male, aged 22. Cardiac enlargement. Apex beat in sixth space in mid-clavicular line. Systolic murmur at aortic area and at apex. Wassermann reaction +. Patient gave a history of 'paralysis' in Salonica in 1916. It was not possible to ascertain the exact nature of the illness. The positive blood reaction suggests that it may have been of syphilitic origin.

Case X. Aortic stenosis. Mitral incompetence. F. A., male, aged 55. Slight cardiac enlargement. Rough murmur over second right costal space close to sternum and accentuated second sound. Syphilis in India twenty years before. Wassermann reaction negative.

Case XI. Aortitis. H. C., male, aged 38. Mild angina attacks. Aortic systolic murmur, with accentuated second sound. X-ray showed general dilatation of whole arch of aorta, uniform in character. Syphilis in India fourteen years ago. Wassermann reaction negative.

Case XII. Aortic stenosis. W. J. B., male, aged 48. Slight enlargement of the heart. Systolic murmur at aortic area with accentuated second sound. Signs of old iritis, perforation of nasal septum, and glossitis. Syphilis in 1892. Wassermann reaction—no record.

Case XIII. Aortitis. T. G. F., male, aged 28. Considerable cardiac enlargement. Precordial pulsation. Also visible pulsation in vessels in neck. Right pulse greater than left. Double murmur at aortic base. Mitral systolic bruit. X-ray, slight swelling in region of aortic arch. History of 'rheumatism' seven years before. No history of syphilis. Wassermann reaction + +.

Case XIV. Aortic incompetence. R. H., male, aged 21. Considerable cardiac enlargement. Double aortic murmur with a Flint's murmur at the apex. History of scarlet fever when 7. None of syphilis. Wassermann reaction negative. This man went through eleven months' training in England in the infantry. He was stopped on a draft because of his heart.

Case XV. Aortic incompetence. J. W., male, aged 38. Much enlargement of heart. Pulsation in praecordium and to right of sternum. Double aortic murmur. Apical systolic murmur. Rheumatic fever when 31. Wassermann reaction negative.

Case XVI. Aortic incompetence. H. B., male, aged 38. Considerable cardiac enlargement. Apex beat in sixth space, one inch external to mid-clavicular line. Aortic diastolic murmur. Rheumatic fever when 9. Rejected for army because of heart, which patient had known to be 'weak' for years. Notwithstanding the aortic disease, and the existence of diabetes, now held in check, this patient continues to carry out his duties in a laboratory. Wassermann reaction negative.

Case XVII. Aortic incompetence. E. A. M., male, aged 25. Cardiac enlargement. Apex beat diffuse. Maximum impulse in sixth space just external to mid-clavicular line. Double murmur at aortic base, with some extra-cardial (? pericardial) accompaniments. History of rheumatic fever. Wassermann reaction negative.

Case XVIII. Aortic incompetence. C. H., male, aged 35. Considerable enlargement of the heart. Apex beat in sixth space, one inch outside the mid-clavicular line. Systolic murmur at apex; double murmur at aortic base. History of rheumatic fever. Wassermann reaction negative.

Summary. Aortic cases.

Of eighteen cases of aortic disease thirteen gave a history of syphilis, or a positive Wassermann reaction, or both.

The ages were 46, 47, 38, 21, 36, 35, 39, 43, 22, 55, 38, 48, 28. The last gave an indefinite history of rheumatism also.

Five cases aged 21, 38, 38, 25, 35, with a negative Wassermann reaction, had a history of rheumatic fever in four instances, and of scarlet fever in the other.

While the number of patients examined was admittedly small, and the conclusions therefore to be drawn cannot be so definite, the results are more akin to the findings of Boyd Campbell (38)—in whose series of twenty-five cases with aortic lesions there was only one negative Wassermann reaction, and in that one patient there was a definite history of rheumatism—than to the figures given by Lewis (39).

The latter writer says that of sixty-six aortic cases only eight gave a positive Wassermann reaction or a history of syphilis, and those were for the most part men over 40. Eight of the above series of thirteen 'positives' were under 40. Dilatation of the aorta or actual aneurysm he also states is rare, only half a dozen cases among some 5,000. He attributes aortic disease to rheumatic fever or chorea in fifty-four per cent. of the cases.

2. *Mitral Stenosis.*

The incidence of rheumatic fever and chorea in the causation of mitral stenosis is placed at sixty-five per cent. by Lewis (39). It is generally recognized that there are a large number of cases of uncertain aetiology.

How far may syphilis be responsible? Cowan and Fleming (40) have adduced considerable evidence to suggest that mitral stenosis and renal fibrosis may in many instances have a common cause, and that some examples of the

combination may be due to syphilitic infection. Fifteen cases of mitral stenosis were investigated. Seven gave a history of one or more attacks of rheumatic fever, one a history of rheumatism, one of chorea on two occasions, one of diphtheria, and in two instances no history of previous illness was obtained. Three patients gave a positive Wassermann reaction.

Case I. Mitral stenosis. Wassermann reaction + + + +. G. H., male, aged 31. No history of rheumatic fever or syphilis. When 17 this patient was in hospital and had a presystolic murmur at the apex with a thrill. He was rejected for military service on this account. The condition still existed at the date of examination (April, 1920). The mother of this patient had a 'stroke' at the age of 52, and another at the age of 56, and this may be an instance of mitral stenosis due to inherited specific disease such as Fournier (15, 16) recognized.

Case II. Mitral stenosis. Wassermann + + + +. E. B., female, widow, aged 47. No history of rheumatic fever. Scarlet fever when a child. Patient was married fourteen years but was never pregnant. When twenty-four years of age she had an illness in which her throat was sore and during which her hair fell out. Before admission to hospital she had been ill for twelve months. The apex beat was in the fifth space, one inch outside the mid-clavicular line, with a thrill and a double murmur in the mitral area. When first in hospital patient had auricular fibrillation. Here of course the aetiological factor may have been the scarlet fever in early years. On the other hand, there is the suspicious illness when the patient was aged 24 and the fact that she never conceived. If the scarlet fever was the cause of the mitral stenosis, the symptoms were an unusually long time in appearing.

Case III. Mitral stenosis. Wassermann reaction + + + +. A. B., female, aged 15. No history of rheumatic fever, chorea, or scarlet fever, or other illness except measles. The apex beat was in the fifth space, one inch outside the mid-clavicular line, with a double murmur and thrill. The family history presented several features of interest. The father of the patient, aged 54, soldiered in India for eleven years, but denied having had venereal disease. Her mother, aged 50, had had fourteen pregnancies. The child born of the first conception is now a woman aged 32. The child of the second pregnancy was a boy who died at five months from 'fits'; that of the third at three years ten months from 'consumption'. The fourth pregnancy resulted in a miscarriage. The child of the fifth conception was a girl who died at twelve months from 'fits'. A miscarriage followed the sixth pregnancy. The child of the seventh pregnancy is now a man, aged 23, who is known to have a syphilitic baby. The patient comes tenth on the list. When much younger she and several of the others attended the Eye Hospital for eye trouble (blepharitis and corneal ulceration). The above history suggests a syphilitic taint, and this may well be a case to be placed in the same category as the first patient in this series.

3. *Mitral Regurgitation.*

None of the sixteen patients suffering from mitral regurgitation gave a positive Wassermann reaction.

Of eight cases of cardiac disorders, other than valvular, investigated, one case of pericarditis with a scarlet fever history and three cases of myocarditis following malaria, influenza, and rheumatism respectively, had a negative Wassermann reaction. On the other hand, the following four cases strongly suggest a syphilitic infection.

Case I. Myocarditis. ? Coronary artery disease. Alternation of heart. H. H., male, aged 50. When first seen this patient showed signs of slight hypertrophy of the heart, with a systolic bruit at the apex and in the aortic area, with alternating strong and weak beats and a 'pulsus alternans'. The blood-serum inhibited haemolysis. When examined again five months later the heart was enlarged slightly as before, with the systolic apical murmur. The alternating strength of beats could not be made out by the stethoscope but was demonstrated on the sphygmomanometer. About every fourth beat was missed at the pulse, and there were occasional extra-systoles. The patient had a history of malaria in 1917, and complained of some precordial pain, with tenderness below the left nipple, and his story suggested mild syncopal attacks. The Wassermann reaction on this occasion was + + + +. The patient's father had served in the army abroad for many years, and his mother had aborted on two occasions. The attack of malaria may possibly have lighted up a latent luetic infection.

Case II. Myocarditis with ? involvement of the auriculo-ventricular bundle. W. H., male, aged 42. Admitted to hospital for pain of an angina-like character at varying intervals, with fainting attacks and shortness of breath on exertion. Previous History: When 12 he had inflammation of the lungs followed by erysipelas, since when he had always had a 'weak' heart. Family History: Patient was not very clear about this, as he has not lived much at home. Both parents died of carcinoma soon after reaching 50 years of age. Two sisters died at four years' interval, each aged 20, one apparently from some cerebral lesion, and the other from some condition in which 'fits' of several months' duration were the most prominent feature. While in hospital the outstanding points in the patient's illness were the bradycardia, pulse 44–48 per minute, of poor quality, and the mild syncopal attacks without actual loss of consciousness. There was definite enlargement of the heart, the apex being $4\frac{1}{2}$ inches from the mid-sternal line and the right border 1 inch to the right. A long, rather rough, systolic murmur was audible at the apex and the base, loudest in the pulmonary area. Wassermann reaction + + + +.

Case III. Myocarditis. H. D., male, aged 40. An old soldier sent to hospital from the Pensions Medical Board as 'D. A. H.' for observation. Complaint: giddiness and shortness of breath and faintness for eighteen months. Previous History: Syphilis in 1903.

Condition while in hospital. Depressed scar on forehead, ? old gumma. Slight cardiac enlargement. Marked tachycardia (140) with extra-systoles. Heart contractions strong, with a poor pulse in comparison. With first mitral sound a faint systolic murmur was heard. Wassermann reaction + + + +.

Case IV. Myocarditis. A. B., female, aged 50. Complaint: attacks of pain in precordial region, and palpitation of some years' duration. Patient had nine children, one of whom died from convulsions, aged 5 months. Also three miscarriages early in her married life. Her husband attended the Eye Hospital six years ago and now suffers from 'nervous debility'. The records of the Eye Hospital show the husband to have suffered from 'keratitis'. The Wassermann reaction was positive, and the condition cleared up under anti-specific treatment. Patient's Wassermann was + + + +. The heart was not enlarged and the action was steady. There was a systolic murmur at the apex.

Series 3. *The Heart Condition in Patients suffering from Syphilis.*

Among thirteen patients of various ages with signs of congenital syphilis in well-marked degree, keratitis, Hutchinsonian teeth, snuffles, &c., only one case was at all suggestive. She was a woman aged 27, with a depression on the

frontal bone, who complained of pain in the region of the aortic arch and shortness of breath. The first aortic sound was replaced by a murmur and the second sound was accentuated. The X-rays did not show any dilatation of the aorta. The patient's serum gave a positive Wassermann reaction, and her brother had died from locomotor ataxia aged 26.

No abnormal signs were discovered in six patients with disease in the primary stage.

Twenty-three patients with secondary syphilis were examined, and one of them showed what was considered to be involvement of the heart. The patient was a man, aged 32, who was admitted to Oxford prison, and, while undergoing the ordinary medical examination, was found to have marked signs of secondary syphilis. He complained of pain over the precordial region, and the cardiac action was very irregular, with many extra-systoles.

After a few weeks' treatment by mercury, the heart condition had markedly improved.

Out of eight cases with tertiary manifestations, one showed signs of a definite change in the heart. The patient was an old regular soldier, aged 48, with a history of a soft sore some years previously, but no clear history of syphilis.

The apex beat was in the fifth space, $\frac{1}{2}$ inch outside the mid-clavicular line. The action of the heart was very irregular, with many extra-systoles, but no murmurs. Some pain down the left arm was complained of.

Under treatment by anti-specific remedies the ulcer of the tongue greatly improved, and the irregularity of the heart's action disappeared, while the apex beat came into just within the mid-clavicular line.

Among five cases of syphilitic infection of the central nervous system, one patient, aged 64, suffering from tabes dorsalis, and giving a history of infection thirty-six years previously, showed gross involvement of the heart.

It was considerably enlarged, the apex beat being one inch outside the mid-clavicular line. There was a mitral systolic murmur and occasional premature contractions. The condition was probably primarily a specific arteritis, including inflammation of the coronary arteries, with a subsequent involvement of the heart.

Twelve patients with a past history of syphilis, but without any outward manifestations, showed no cardiac lesions.

Conclusions.

Syphilitic infection of the heart may occur in the congenital or acquired form of the disease either at an early or late stage.

In this series of cases the anatomical lesions found after death have been :

(*a*) Gumma of endocardium, one instance.

(*b*) Fibrosis of myocardium, one instance.

(*c*) Aneurysmal dilatation of the heart wall, one instance.

(*d*) Thickening of endocardium with coronary artery disease, one instance.

(*e*) Pericardial effusion containing spirochaetes with small gumma under endocardium, one instance.

The clinical picture has included:

(*a*) Disease of the aortic valves. Thirteen out of the eighteen cases of aortic disease investigated (70 per cent.) had evidence of a specific infection: with one exception all the thirteen patients were under 50 years of age, eight being under 40.

(*b*) Disease of the mitral valve—stenosis. Out of fifteen cases, three patients with suggestive personal or family histories had positive Wassermann reactions.

(*c*) A mild degree of the Stokes-Adams syndrome, and also alternation of the heart, has been found. Cardiac enlargement, with extra-systoles, tachycardia, arrhythmia, and a systolic apical murmur have been noted.

(*d*) Sudden death occurred in two patients, in one of whom a gumma of the endocardium was found at autopsy, and, in the other thickening on the septal endocardium.

The heart's action has been noted to be strong in comparison with the pulse.

The symptoms complained of were anginal and fainting attacks with precordial pain and shortness of breath.

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INVESTIGATIONS ON THE CONCENTRATION OF THE NITROGENOUS METABOLIC PRODUCTS IN THE BLOOD UNDER PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

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It has been known for a long time that in certain kidney diseases nitrogenous metabolic products are retained in the organism, but only in the last decade, thanks to the improvement in technique, has it been possible to study the concentration of each metabolic product in the blood under physiological and pathological conditions. With his micro-methods Ivar Bang (1) and, later, many of his pupils have increased our knowledge of a number of the chemical bodies of the blood such as the chlorides, residual nitrogen,[1] urea, fat, &c. Otto Folin has gone farther than Bang with the methods he has continually improved during the last decade, making it possible especially to determine the quantitative relations of the nitrogenous bodies in the blood. In 1913 Folin (2) published his first 'System of Blood Analysis', by means of which a simultaneous estimation of residual nitrogen, urea, and uric acid could be made with a single sample of blood. Later, Folin and several other American workers have described simple methods of estimating the other constituents of the blood, such as creatinin, creatin, &c. This development of the medico-chemical technique has stimulated a number of investigations on the chemistry of the blood, particularly by V. C. Myers (3) and his pupils. In these experiments the quantitative relations of the nitrogenous bodies in the blood in healthy people, and exhaustively also in a number of pathological conditions, have been elucidated. The technique employed, however, was not entirely free from error. The uric acid method usually involved a loss of about 10–15 per cent., and a number of creatinine estimations were carried out by methods which gave too high values (Greenwald and McGuire (4)).

It was further an important objection that a relatively large amount of blood was required for the simultaneous determination of residual N and the better known nitrogenous bodies, more, indeed, than could be obtained from a single patient after much practice. In 1919 Folin (5), in company with his pupil Wu, published a 'System of Blood Analysis', by which it is possible to estimate

[1] Residual nitrogen implies non-protein nitrogen.

residual N, urea, uric acid, creatin, creatinin, and sugar with only 10 c.c. of blood. The sugar method—as the authors (6), among others, have drawn attention to—is not quite accurate, and Folin has subsequently modified it. But apart from this, Folin's last 'System' constitutes a masterpiece in medico-chemical technique. In his uric acid method, particularly, Folin has succeeded in eliminating the difficulties of the method which for a number of years have been the object of futile research.

In the near future Folin's technique will undoubtedly obtain a wide application clinically because its simplicity and the relatively small quantity of blood required make it extremely suitable for the investigation of the concentration of the various nitrogenous metabolic products in the blood under pathological conditions. We, therefore, thought it would be of interest to investigate the nitrogenous constituents of the blood, with the help of Folin's 'System', in a larger number of cases; and we have employed partly healthy people, convalescents, and patients suffering from diseases in which the nitrogenous products in the blood could be presumed to be normal, and partly diabetics and patients suffering from kidney disease. In a number of these, particularly the renal patients, we have further investigated the excretion of phenolsulphonephthalein.

Before beginning our investigations we undertook a number of analyses of solutions of pure urea to control the residual N and the accuracy of the urea method. Of these controls the following may be tabulated:

A 1 per cent. urea solution was prepared. This was analysed by the residual N method, and also by the urea method.

The *residual N method* gave the following results in three estimations:

1. 0·474 pro mille N
2. 0·465 „ „ „
3. 0·455 „ „ „

} Calculated, 0·466 pro mille.

The *urea method* gave the following results in three estimations:

1. 0·454 pro mille N
2. 0·467 „ „ „
3. 0·471 „ „ „

} Calculated, 0·466 pro mille.

An estimation of the residual N in the blood was next made before and after the addition of a definite amount of urea.

Blood, 1. Residual N. In two analyses 0·392 pro mille was found both times. The same blood, with the addition of 1 pro mille urea, gave 0·89 against 0·86 pro mille calculated.

Blood, 2. Residual N. In two analyses 0·44 and 0·43 pro mille were found. The same blood, with the addition of 1·41 pro mille N in the form of urea, in two estimations gave 1·87 and 1·82 against 1·83 and 1·84 pro mille calculated.

From these controls it follows that Folin's residual N and urea methods are very accurate, as the error does not exceed 3–4 per cent.

The result of the sugar estimation in the blood, as mentioned above, is not absolutely accurate. The following estimations were made, however, before we

were aware of the error of the method, but since it is not great we have included the results obtained.

TABLE I.*

Healthy People and Patients suffering from Various Diseases.

Name.	Sex.	Age.	Diagnosis.	Residual N.	Urea N.	Urea.	Creatinin.	Sugar.	Phenol-sulphone-phthalein.
E. B.	M	22	Nil	28·7	11·5	2·4	—	110	
E. K.	M	24	,,	31·4	13·9	4·1	1·0	109	60
M. H.	F	28	,,	36·0	18·9	3·9	1·2	98	
H. M.	M	26	,,	26·9	10·5	3·3	1·2	111	
H. B.	M	54	Cancer	32·0	14·2	4·3	—	109	
A. B.	M	45	Pernicious anaemia	33·1	11·8	4·6	1·1	110	
J. A.	F	62	,, ,,	23·7	16·2	2·8	1·1	105	80
P. N.	M	41	,, ,,	30·9	19·7	—	1·0	100	
O. B.	F	39	,, ,,	26·9	15·1	4·0	1·0	106	
O. S.	M	58	Polyneuritis	30·8	11·5	2·5	1·1	100	
G. A.	M	60	Abdominal tumour	37·8	22·2	3·6	1·2	145	
K. S.	M	25	Sciatica	34·0	14·2	2·5	—	105	
O. R.	M	30	Tuberculous peritonitis	39·0	19·2	2·8	1·3	100	
M. E.	M	70	Cancer	41·0	20·9	3·3	1·1	134	

* The figures for the nitrogenous constituents and for the sugar represent, in all the tables, milligrams per 100 c.c. blood.

In healthy people, and in patients suffering from various diseases in whom the nitrogenous substances of the blood *a priori* were presumed to be normal, we have found (in fourteen individuals) the following limiting values, as will be evident from Table I:

	Minimum.	Maximum.	
Residual N	23·7	41	Mg. per 100 c.c. blood
Urea N	10·5	22·2	,, ,, ,,
Uric acid	2·4	4·6	,, ,, ,,
Creatinin	1·0	1·3	,, ,, ,,

The values agree, on the whole, quite well with those found previously. The range of variation of the urea N, however, is rather larger than is usually seen. Similarly, the upper limit of the normal uric acid concentration is higher than hitherto assumed. Folin points out that his latest method gives higher values than the earlier ones, and he thinks it is because some uric acid was lost in the earlier methods. We have not found a greater creatinin concentration than 1·3, while many earlier investigators (Folin (7), 1914, and Myers (8), 1916) found up to 2·5 in healthy individuals.

In eight diabetics (see Table II), in some of whom the blood-sugar was considerably increased, we found the concentration of the nitrogenous bodies in the blood to be normal, with the exception that the uric acid concentration in one case rose to 5·8, and that the creatinin values on an average were much greater than normal, but lower than the upper limit fixed by Folin and later by Myers.

TABLE II.

Diabetes.

Name.	Sex.	Age.	Residual N.	Urea N.	Uric Acid.	Creatinin.	Sugar.
A. H.	F	20	26·4	11·3	1·8	1·5	286
—	—	—	24·1	8·9	1·9	1·4	276
S.	M	65	lost	13·5	1·3	1·5	109
J. S.	M	55	27	13·3	2·2	1·5	113
O. H.	F	45	33·3	17·0	3·6	1·4	200
M. O.	F	55	34·3	15·2	3·2	1·6	267
I. J.	M	22	24·6	12·1	2·8	1·3	298
S. F.	F	18	34·3	12·1	5·8	lost	250

TABLE III

Renal Disease.

Name.	Sex.	Age.	Diagnosis.	Blood-pressure.	Residual N.	Urea N.	Uric Acid.	Creatinin.	Sugar.	Phenol-sulphone-phthalein
G. O.	F	43	Nephrosis	110	33·2	18·1	2·3	1·2	113	65
G. S.	M	17	„	115	28·3	9·2	3·8	1·0	109	80
H. S.	F	54	„	110	27·5	13·0	2·3	1·9	95	73
A. J.	F	57	Nephro-sclerosis	165	40·0	19·5	2·2	1·7	97	53
S. J.	F	78	„	210	39·1	14·0	4·0	1·2	137	—
A. B.	F	54	„	200	36·6	17·0	3·6	1·6	93	60
J. H.	M	26	Nephritis	130	37·1	15·8	5·2	—	114	46
„	—	—	—	—	34·3	11·8	6·1	—	108	—
O. T.	M	22	Nephritis	135	31·2	11·8	4·5	—	106	70
R. P.	M	20	„	135	29·5	16·6	3·6	—	122	64
I. K.	F	22	„	130	52·0	38·2	3·0	1·3	97	26
„	—	—	—	—	48·9	34·4	2·3	1·8	102	—
A. S.	M	30	Nephritis	115	37·1	17·8	5·1	1·5	95	—
„	—	—	—	—	32·3	13·7	2·9	1·2	100	—
E. R.	M	40	Nephritis	115	35·0	16·6	4·0	1·1	102	—
A. F.	M	36	„	120	40·0	16·8	3·2	1·3	93	—

In the diagnosis of kidney disease (see Table III) the classification devised by Volhard and Fahr (9) has been used. Like all other classifications this has its limitations, partly because nature is not schematic but displays all possible intermediate forms. On the whole, however, Volhard and Fahr's classification of renal diseases is undoubtedly a great step forward, as is fully proved by the wide recognition their work has received in the course of a few years from almost every quarter.

In three patients suffering from nephrosis and three suffering from nephrosclerosis the nitrogenous bodies were found to be normal in concentration.

Of the seven nephritis cases, six were getting well again. In these the residual N and urea values were normal, but two of them showed some increase in the amount of uric acid. One patient, I. K., showed symptoms of chronic nephritis in the second stage, and in her case a considerable increase of residual N and urea N was found in two tests, while the uric acid and creatinin concentrations were normal.

Myers and his pupils contend the kidneys are able to concentrate creatinin much more easily than uric acid, urea occupying an intermediate position, from

which one would expect uric acid would be the first to be retained when the kidneys became impaired in function, followed by urea—and creatinin not until the disease was farther advanced. In the extensive material dealt with by Myers and his pupils there appears to be a 'staircase effect' when the blood analyses of nephritis patients, whose disease is fairly well advanced, are compared. There are exceptions to the rule, however, since—as Myers himself points out—nephritis cases occur with retention of residual N and urea N but no increase of uric acid. As already mentioned we had two among the seven patients who showed an increase of the uric acid concentration only, while one had an increase of residual N and urea N, but not of uric acid. The phenolsulphonephthalein excretion was considerably lowered in the patient with increased residual N and somewhat low in the patient J. H., who had an increase of uric acid only.

In addition to the above investigations in a total of thirty-four healthy and diseased people, we have had the opportunity of following the concentration of the nitrogenous metabolic products in the blood for a longer period, until death took place, in four patients who suffered from various kidney diseases, but all of whom had typical symptoms of uraemia.

TABLE IV.

No. 1. O. O. Man, 32 years old. Diagnosis: Pyelonephritis.
Admitted May 7. Died May 18.

Day.	Residual N.	Urea N.	Uric Acid.	Creatinin.	Sugar.	CO_2 in Blood.	Blood-pressure.
May 10	220·0	167	8·6	20·3	0·14	—	150
„ 12	251·6	197·3	8·7	20·5	0·14	—	—
„ 14	272·4	235	—	22·0	0·14	—	160
„ 17*	300	250	10·5	23·0	—	20	—

* Sixteen hours before death.

The first of these patients was a man, 32 years old, whose mother and brother had died of tuberculosis. At the age of 14 he had tuberculosis of the spine, and ten years ago he was in Molde Hospital with 'kidney disease', from which he is said to have recovered. He was then well until two months before admission to hospital, when he became increasingly short of breath, oedema appearing at the same time.

On admission, 7.5.20, he was pale, rather oedematous, and complained of headache. Albumin, masses of pus cells, and numerous staphylococci were found in the urine, but no casts. He vomited frequently and was rather restless, but had no fits. The blood-pressure was 130–150. During his last days he became comatose, dying in coma on 18.5.20. The amount of urine for the first week was 500–600 c.c., but then sank to 300 and 200 c.c. During the last twenty-four hours the patient passed no urine. Double pyelonephritis was found at the autopsy.

The blood of this patient was tested for the last eight days before death. As will be seen from the first test, the residual N was already 220 mg. and increased steadily until, about twelve hours before death, it reached a value of 300 mg. The urea increased parallel with the residual N, the first value being 167 mg. and the last 250 mg. The amount of uric acid rose from 8·6 to 10·5 mg. The creatinin in the first test was already unusually high, 20·3 mg., and rose to 23 mg. The alkali reserve was investigated once only, at the last blood test

twelve hours before death. It was then 20; that is to say, as low as it is found in diabetic coma. Therefore 25 grm. sod. bicarb. were administered by the mouth, divided into several doses, which he retained, but it did not seem to have any influence on his condition.

TABLE V.

No. 2. A. B. Man, 42 years old. Diagnosis: Malignant nephro-sclerosis. Admitted May 19. Died May 26.

Day.	Residual N.	Urea N.	Uric Acid.	Creatinin.	Sugar.	CO_2 in Blood.	Blood-pressure.
May 21	132	112	7·6	10·0	0·12	46	$\frac{260}{180}$
„ 22	160	134	7·6	12·8	0·125	51	—
„ 24	240	200	7·5	19·2	0·133	41	$\frac{250}{150}$
„ 25 8 a.m.	275	253	8·3	21·2	0·137	37	200
May 25 7 p.m.	304	265	—	21·5	—	28	—
May 26 8 a.m.	320	270	9·5	22·0	0·146	30	—
May 26* 6 p.m.	320	280	9·0	26·8	—	30	210

* Five hours before death.

Patient No. 2 was a man 42 years of age who had a marked tuberculous taint in his family, four of his brothers and sisters having died of tuberculosis. He himself had been well up to the summer of 1918, when he began to get headache, which later became almost incessant and tended to get worse. He was admitted to the medical wards on two occasions—six weeks in the spring of 1919 and seven days in May, 1920.

During his first stay in hospital he had a greatly increased blood-pressure, 230–250, and a trace of albumin and casts in the urine. The headache and albumin disappeared in hospital. After autumn and winter the headache started anew, but he was at work in an office up till four days before admission to hospital. During his second stay in hospital the most important symptoms were headache, vomiting, apathy, sleepiness, and coma which ended in death. An autopsy was not allowed. There was no oedema and no fits. The urine contained considerable quantities of albumin as well as red blood-cells and casts. The amount of urine, as appears in the table, was seen in the first few days much decreased, and during the last days none was passed. Its volume, specific gravity, and content of sodium chloride and urea were as follows:

Date.	Amount.	Sp. gr.	NaCl %.	Urea %.	
May 21–2	180 c.c.	1025	0·92	2·14	
„ 22–3	230 „	1012	0·16	1·15	catheter
„ 23–4	195 „	1011	0·19	1·05	„

In November, 1919, one of us (Höst) estimated the residual N, which was normal, but on admission it was, as will be seen, considerably increased and rose in the course of the following five days extremely rapidly, being 320 mg. five hours before death. The urea N ran parallel with the residual N and reached a value of 280 mg. The uric acid only rose from 7·6 to 9 mg., but the creatinin increased rapidly from 10 to 26·8 mg. The alkali reserve sank from about normal to roughly 30, and the blood-pressure, which in the first few days was about 250, declined during the last days to 200.

The third patient was a woman of 54, who had previously been healthy. but three months prior to admission began to feel languid and tired, and suffered from thirst. During the ten days she was in hospital the most important

symptoms were dyspnoea, headache, nausea, vomiting, sleepiness, and coma ending in death. The urine contained albumin and casts but no red blood-cells. There was no oedema and no fits. The blood-pressure was about 200. The amount of urine for the first few days was 500–600 c.c., but sank towards the end to a couple of hundred. No autopsy was allowed.

TABLE VI.

No. 3. M. H. Woman, 54 years of age. Diagnosis: Malignant nephrosclerosis.
Admitted July 3. Died 13.7.20.

Day.	Residual N.	Urea N.	Uric Acid.	Creatinin.	CO_2 in Blood.	Blood-pressure.
July 11	100	85	4·0	6·0	30	200
„ 12	144	130	4·6	10·8	30	210
„ 13* 9 a.m.	213	200	10·0	20	30	200

* Two hours before death.

The nitrogenous constituents of the blood were investigated during the last three days the patient was alive. The last sample of blood was taken two hours before death. All the nitrogenous substances rose very rapidly, but the residual N and the urea N did not reach such high values as in the preceding patients. The alkali reserve was in this case also down to 30.

TABLE VII.

No. 4. M. F. Man, 21 years of age. Diagnosis: Chronic nephritis.
Admitted, first time 7.2.20. Discharged 7.5.20.
„ second time 10.10.20. Died 24.11·20.

First Admission to Hospital.

Day.	Residual N.	Urea N.	Uric Acid.	Creatinin.	Blood-pressure.
Mar. 23	69	47	1·9	2·1	135
Apr. 7	72	45	2·7	3·0	—
„ 23	75	60	—	3·0	150
„ 30	77	60	5·0	3·0	140

Second Admission to Hospital.

Day.	Residual N.	Urea N.	Uric Acid.	Creatinin.	CO_2.	Blood-pressure.
Oct. 11	235	188	8·4	10	44	150
„ 14	240	190	10	10	36	150
„ 16	240	200	9	10	36	—
„ 21	236	194	10	9	46	140
„ 25	235	205	13	9	29	30 grm. sod. bicarb. from
					7 o'clock 54	11 to 6 o'clock
„ 28	230	200	12	10	52	150
Nov. 5	240	203	12	9	48	—
„ 12	256	210	14	9	42	150
„ 15	265	215	17	9	40	—
„ 18	341	271	19	14	50	150
„ 23	335	275	26	19	50	150
„ 25*	350	279	26	20		

* Twenty-four hours after death.

The last of these patients has been the best observed, and therefore possesses the greatest interest. It was a man, 21 years old, who was twice in hospital—three months in the spring of 1920 and six weeks in the autumn of the same

year. He had been well till three or four weeks before the first admission, when he began to suffer from tiredness and thirst, for which he consulted a doctor, who discovered albuminuria. During the first stay in hospital the patient had no other symptoms than tiredness, apart from albuminuria, haematuria, casts in the urine, and a rather increased blood-pressure, 130–150.

The nitrogenous bodies of the blood were estimated four times during the first stay in hospital, and showed, as may be seen, on the first test somewhat increased residual N and urea, but the uric acid and creatinin were normal. The three following determinations showed a distinct but not a very great rise in the amounts of all the constituents, the uric acid and creatinin exhibiting a pathological increase.

On discharge from hospital, May 7, 1920, the patient was fairly well and was able to do some work for four months. In the beginning of September he again had to give up work on account of feeling languid and increasing oedema. The most important symptoms during the second visit to hospital were oedema, marked dyspnoea, continual vomiting, headache, pericarditis, dry pleurisy, and retinitis. The urine contained albumin in varying quantities, casts, and now and again blood. In the last few days of life the patient became somnolent and died in coma. At the autopsy, double contracted kidney was found.

The blood examinations showed that the nitrogenous bodies remained almost unchanged in the first month, but increased very rapidly in the last ten days and, as will be seen, reached very high values. Twenty-four hours after death an autopsy was made, and blood was collected from the heart which, on analysis, was found to contain the same quantities of residual N, urea, uric acid, and creatinin as the blood taken immediately before death. The demonstration that the nitrogenous constituents of the blood are not altered in the first twenty-four hours after death is of no small interest because it renders the diagnosis of uraemia possible after death. The alkali reserve differs somewhat from the other cases. In the first fortnight it varied between 36 and 44, and when, on October 25, it had fallen to 29 the patient received 30 grm. sodium bicarbonate between 11 and 6 o'clock. At 7 o'clock another test showed the alkali reserve had risen to 54, and remained stationary for the whole of the next month at about 50.

The urine of this patient was interesting. From October 14, until the patient died, the amount of urine, the specific gravity, urea, and chlorides were daily recorded. The quantity of urine passed daily from October 14 to November 10 was between 1 and 2 litres, but on November 11 it suddenly dropped to 500, and later it reached from 200 to 300 c.c. per diem. As will be seen this fall in the diuresis coincides fairly accurately with the rapid increase in the nitrogenous bodies of the blood. The specific gravity of the urine during the whole of the second stay in hospital was 1,010–1,011, that is to say, it had the same molecular concentration as the blood. The patient showed signs of hypostenuria or, as it has also been called, isostenuria, which, as is well known, is characteristic of the third stage of nephritis. The concentration of urea in the urine varied from 0·8 to 0·2 per cent., rising somewhat in the last week of the patient's life. The chloride concentration showed just the opposite, being about 1 pro mille at first, but during the last week it fell to 0·2 to 0·3 pro mille.

Our investigations on the nitrogenous bodies of the blood in uraemia comprise, as will be seen, only four patients, but the results should nevertheless be of interest because each patient had been examined fairly thoroughly.

Only with the aid of Folin's methods has it been possible to determine the residual N, urea N, uric acid, and creatinin simultaneously in a small sample of blood, and therefore the majority of estimations previously carried out in Europe, and especially Germany, relate only to a few nitrogenous bodies in the blood. In America a considerable number of investigations on the chemistry of

the blood in uraemia have been undertaken in the course of a few years, especially in Myers' laboratory at the Post-Graduate Hospital, New York, but the patients were, as a rule, not followed from day to day up till death, as we have done.

It would be interesting to know whether the results of these tests throw any light on the various problems connected with uraemia, and we will therefore proceed to discuss our investigations with reference to the cause of the marked accumulation of nitrogenous metabolic products in the blood in uraemia, and see if our material affords any basis for a causal relation between the accumulated products and the uraemic symptoms. When metabolic products are retained in the body the cause may be a diminished excretion, an increased formation, or a combination of the two. In uraemia we know that in consequence of renal disease there is deficient excretion. Our material also illustrates this point, as there was always a marked diminution in the amount of urine or even anuria preceding or running 'parallel 'with a pronounced increase of the nitrogenous metabolic products in the blood.

Some authors, such as Richter and von Noorden (10), maintain, however, that in uraemia a considerable increase in the production of nitrogenous bodies can take place, which they believe to be due to a greatly increased breaking down of the tissue proteins in consequence of the uraemia. In three of our uraemia patients we have tried to obtain an explanation of the amount of urea formed in the body. In such an inquiry it is necessary to know the amount of urea the patient normally produces on the given diet, the quantity of water in his tissues, the relation between the amount of urea in the blood and the total amount in the body, and the quantity of urea excreted.

We know that an adult on an ordinary diet excretes 15–30 grm. urea in twenty-four hours, but while fasting the excretion is much smaller, and our uraemic patients' diet closely approximated to the latter, because only small quantities of sloppy food and water were taken on account of nausea and vomiting. In order to guard against too low an estimate of the production of urea we have adopted a daily value of 15 grm.

The second factor, the water content of the organism, is comparatively well known under physiological conditions, but in uraemia, where water is retained, the estimation of the total fluid content is very uncertain.

As regards the relation between the urea concentration of the blood and tissues, Marshall and Davis (11) were probably the first to show that urea is not accumulated in the blood only, but is found fairly evenly distributed in the organism, which has later been confirmed by many others.

It is only the fourth factor, the excretion of urea, that can be accurately determined, provided the patient has no diarrhoea which would occasion the excretion of large amounts of urea by the intestine.

There are therefore various difficulties in the way of determining the amount of urea formed in uraemia, and it can only be large deviations from the normal that there is any hope of demonstrating by such estimations.

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In patient No. 4 the daily excretion of urea was determined. If we take the last fourteen days the patient lived for the purpose of calculation, when the greatest increase of the urea in the blood was found, we obtain a urea excretion of 60 grm. altogether. If it is assumed that under physiological conditions 15 grm. of urea would be formed in twenty-four hours, then for fourteen days the amount works out at 210 grm. The 60 grm. excreted by the patient must be subtracted from this, leaving about 150 grm. urea as the amount retained by the patient in this fortnight. The total volume of fluid in this patient was difficult to estimate on account of the oedema, but as his weight was 65 kg. the fluid in his body may be reckoned as about 50 kg. 150 grm. of urea contain about 70 grm. urea N, and this 70 grm. N distributed over 50 kg. fluid corresponds to 120 mg. N per 100 c.c. blood. As will be seen the residual N of the blood rose about 70 mg. in this fortnight, which agrees fairly well with the calculated amount when it is considered the calculation is made for the whole period of fourteen days, and consequently a trifling error each day will add up to a considerable one.

Patient No. 2 weighed 65 kg., and as he had no oedema his total volume of fluid can be estimated at about 40 kg. During the period May 21–24, that is to say, immediately before he died, the daily excretion of urea was determined and was found to be 8·55 grm. Assuming again a daily urea production of 15 grm., the amount retained was $15 \times 3 = 45 - 8{\cdot}55 =$ about 36 grm. urea, corresponding to about 16·8 grm. N. 16·8 grm. N in 40 kg. fluid is roughly 42 mg. per 100 c.c. blood. As a matter of fact the urea N in this period rose from 112 to 200 mg., that is, 88 mg., in other words twice as much as calculated. This patient therefore had a very marked production of urea.

The blood of patient No. 3 was tested during the last three days of life. The last sample was taken two hours before death. No urine was passed in the last twenty-four hours, and in the previous twenty-four hours the amount was only 200 c.c. The excretion of urea in the last two days was therefore extremely small and can be neglected in the calculations. The patient weighed 65 kg. and had no oedema. Reckoning in the same manner as before, the urea N in the blood during these two days should have risen about 35 mg., but in reality it increased 115 mg., therefore more than three times as much as calculated. A similar marked increase took place in the case of residual N, uric acid, and creatinin.

It is clear the accumulation of urea in the organism in cases of uraemia proceeds with very different rapidity, and this is only dependent upon its excretion in a very subordinate degree. As the nourishment taken by these patients during the period of observation was practically the same, and was decidedly insufficient for the needs of the body, the varying rapidity with which the accumulation took place must have been to a large extent due to the fact that the patients metabolized their body proteins in very different degrees.

The reason why a considerably greater breaking down of protein occurs in some uraemic patients than in others is not at first sight clear. But we must not omit to point out the fact that in the patient in whom the urea production

corresponded so well with the calculated quantity there was hardly any acidosis, while in the two others, in whom it was strikingly large, there was marked acidosis. In this connexion we must remember Senator's view that in uraemia abnormal protein metabolism is going on with consequent acidosis. How far this conception is true we are not in a position with our scanty and, as far as this question is concerned, too superficial investigations, to give an opinion.

The other question—how the results of our investigations harmonize with a causal relation between the accumulated metabolic products in the organism and the uraemic symptoms—will now be shortly discussed. It is still uncertain whether the nitrogenous products are the cause of the uraemia or whether the latter is due to unknown substances. Numerous investigations, partly experimental on animals and partly clinical, dealing with the rôle of the various nitrogenous bodies in uraemia, have failed to solve the problem with any degree of certainty. But it is probable that one or more of the bodies is directly responsible for uraemia. If the amount of the various nitrogenous bodies in the blood of our cases be followed daily during the last days or weeks before death, that is, at the time when the clinical symptoms steadily got worse, it will be noticed that the uric acid is considerably increased in all, but in two of the patients it shows no upward tendency, while in patient No. 4 it rises very rapidly in the last week.

Myers has contended that in renal insufficiency the uric acid as a rule is the first of the nitrogenous substances to be retained, as previously mentioned. Our investigations seem to show that in advanced uraemia the uric acid concentration in the blood is not so pronounced as that of the other nitrogenous constituents, which may possibly be due to the fact that the formation of uric acid is normally considerably less than the formation of creatinin, and especially urea, and therefore when the excretory power of the kidney is further reduced the retention of the creatinin and urea exceeds that of the uric acid. The concentrations of residual N, urea N, and creatinin, on the other hand, are increased continuously right up till death. In patient No. 3 the amounts of residual N and urea N were decidedly less than in the other patients, the figures being 213 and 200 respectively, while in the three others they were 350–300 and 280–250 respectively. It is interesting to note the large fraction of the residual N constituted by the urea N in this patient. It has long been known that with increase of residual N the percentage of it constituted by urea N also rises simultaneously. The fact that this relation is particularly well marked in this patient, who died with a lower concentration of residual N in the blood than the other patients, but in whom the concentration of the nitrogenous bodies in the blood rose *more rapidly* than in any of the other patients, might indicate that the rate at which this substance increases in the blood influences the relation between residual N and urea N.

It is well known that death in uraemia can take place with varying quantities of residual N and urea in the blood, but it does not necessarily negative a causal relation between the nitrogenous products and uraemia. The resistance of the

organism against intoxication may be different, and thus the duration of the intoxication may be important in this connexion. The most constant factor in our patients was the marked increase of creatinin just before death, which agrees with Myers' observation that the amount of creatinin is the best indication of the condition in uraemia.

The alkali reserve in all our patients was diminished sometimes very considerably. In patient No. 4, after the administration of sodium bicarbonate, it rose again to about the physiological concentration and was roughly normal during the whole of the last month of life, that is to say, at a time when the most important increase of the nitrogenous bodies took place. The fact that death ensues with the typical picture of uraemia while the alkali reserve is absolutely normal—although it was so only in the case of one patient, the others exhibiting a considerable diminution of the alkali reserve—shows that acidosis cannot be of great significance in the aetiology of uraemia.

Our material is too small to allow of any decisive conclusion on the rôle of the retained nitrogenous bodies in the aetiology of uraemia. But the pronounced parallelism there has been in our four patients between the increasing concentrations of the residual N, urea N, and creatinin on the one hand and the clinical symptoms on the other, supports the assumption that there is a causal relation between the retained nitrogenous metabolic products and the clinical symptom-complex, uraemia.

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SOME ASPECTS OF EXOPHTHALMIC GOITRE[1]

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In 1910 Hale-White (1) published a paper on all cases of exophthalmic goitre treated at Guy's Hospital between the years 1888 and 1907. His special object was to establish the prognosis of medical treatment, so that one could decide clearly whether surgical treatment improved the prognosis.

This paper deals with all cases of exophthalmic goitre treated in the wards between the years 1908 and 1917, and I wish to thank the physicians and surgeons of Guy's Hospital for allowing me to refer to cases who have been under their care. The reports of one hundred and twenty-seven cases were available, and of these I was able to trace eighty-nine till the time of their death, or for varying intervals after the onset of their disease—sometimes for sixteen and never for less than four years. While abstracting these reports it seemed worth while to record certain facts as regards the signs and symptoms and aetiology of the disease, and for this purpose all the cases are included.

Signs and Symptoms.

Of the cases, one hundred and ten have been grouped together as true exophthalmic goitre and seventeen as hyperthyroidism. In fifteen of the latter the symptoms came on gradually, many years after the development of an enlarged thyroid, which had previously given rise to no symptoms; and in two severe mitral stenosis had been present for many years before any other symptoms. Of those seventeen cases exophthalmos was absent in five, recorded as slight in five, and very slight in seven; the tremor was absent in six, and recorded as slight in six; the pulse-rate was only over a hundred in six; and loss of weight and excessive sweating were unusual, and there was no case of diarrhoea or of glycosuria.

In all these points, and in others to be mentioned later, the group differs from the cases classified as exophthalmic goitre. Of these latter 93 per cent. had exophthalmos (in 25 per cent. it was recorded as slight); 99 per cent. had enlargement of the thyroid (10 per cent. slight); 96 per cent. had tremor (16 per cent. slight); 78 per cent. had a pulse-rate of over 100 and 22 per cent. had

[1] Part of a thesis accepted for the D.M. degree in the University of Oxford.

[2] Under the tenure of the Hilda and Ronald Poulton Fellowship, Guy's Hospital.

a pulse-rate between 80 and 100 when at rest in bed. In the great majority of cases these four cardinal signs and increased metabolism are all present at some time during the course of the disease.

Of other well-known signs it is more difficult to speak in a paper based on the study of reports which are not always complete. Even so, increased excitability in some form or other is recorded in 82 per cent., excessive sweating in 76 per cent., and loss of weight in 74 per cent. Probably these signs are really present in almost as high a proportion of cases as are the four cardinal signs.

Diarrhoea. This is mentioned as occurring in twenty-six of these cases. It is interesting, as diarrhoea is generally associated with increased tone of the para-sympathetic system, while most of the signs are associated with increased tone of the sympathetic system.

Amenorrhoea. In this series there are notes on thirty-one cases. In eight of these the periods were said to be regular. In nineteen there were amenorrhoea, and in twelve of these it was of over nine months' duration. In only four was there dysmenorrhoea or menorrhagia.

Pyrexia. This was generally found in those cases who died apart from any obvious source of infection. In some moderate pyrexia lasted for one or two weeks; in others there were sharp rises for a few hours occurring at quite irregular intervals. The same rise is often found after operations on cases of exophthalmic goitre, and in all these cases the explanation is probably a sudden large overdose of thyroid substance. With the rise in temperature the general symptoms become worse and mental symptoms are specially liable to be aggravated. There appears a close resemblance to the hyperpyrexia which may be produced by β-tetrahydronaphthylamine (7), and the mechanism of this experimental 'sympathetic fever' throws light on the other.

A close comparison has been drawn between this 'sympathetic fever' and the events occurring in heat-stroke. It is interesting in this connexion to recall Crile's treatment in the hyperexia following thyroidectomy. With ice-packs and treatment very similar to that adopted in cases of heat-stroke, he has recorded very successful results.

Symptoms of hypothyroidism. Some cases have been described where symptoms of hyper- and hypothyroidism have been present together. These are difficult to explain if the disease really depends simply on hypersecretion of a normal product.

There are other cases where an attack of exophthalmic goitre has resulted in myxoedema. These have been most common after prolonged X-ray treatment, but have occurred apart from this.

Among the cases who were seen in this series none had developed definite myxoedema, but two had signs somewhat suggestive of it. In both these exophthalmos still persisted, and in one there was persistent tachycardia, presumably due to organic changes produced in the heart.

Probably most of the cases which have been described as showing symptoms of hyperthyroidism and hypothyroidism are really of this type, some of the

organic signs of the hyperthyroidism persisting after the functional hyperthyroidism has passed away.

Mental characteristics. It has long been recognized that many patients with exophthalmic goitre are specially prone to develop mental disorders. The majority show some mental changes during their illness, and are not as easy to deal with as other patients.

In this series rather more than one-tenth developed more acute mental symptoms—in three cases sufficiently serious to be diagnosed as acute mania or acute confusional insanity. These symptoms were in general of specially serious import; though one patient, who suffered from acute confusional insanity, had been in regular work eight years after the onset of her illness.

Fits, probably hysterical, and hysterical attacks were frequently mentioned in the account of previous illnesses, and in at least one case they had occurred regularly each month for many years.

Two cases of those who could be traced ended in an asylum—one with a diagnosis of dementia praecox, and one with a doubtful diagnosis of chronic epilepsy. In both these cases there was a gradual change from the typical picture of exophthalmic goitre to the final picture of mental disorder, with a gradual loss of most of the earlier physical signs of the disease. There was never any sudden change or any period of good health in between, and no one would have made any diagnosis other than exophthalmic goitre in the early stages.

There are many cases on record where all the signs and symptoms have developed rapidly after fright or other emotional disturbances. In the majority of these cases, especially among the younger, the onset was sudden, and all signs and symptoms were well marked within two months of the onset of any illness. In a smaller number the onset was very sudden, the whole illness developing in a few days.

Of cases showing a very acute onset there are some examples. One of these recovered entirely and appeared absolutely normal, mentally and physically, and led a very strenuous life. Her symptoms developed after her fiancé was torpedoed and drowned, the news of which was brought to her without any warning by a small boy. She had not referred to this while in hospital, but was quite ready to talk of it when she had recovered.

In a small proportion of cases the disease follows a serious emotional disturbance; in a larger proportion it follows an emotional disturbance which would be passed through without difficulty by the normal subject. The disturbance can only be regarded as an exciting cause; the liability to the disease depends on something more fundamental in the individual's constitution. In cases where the exciting cause is trivial the prognosis is probably worse than in other cases.

Duration of illness. This is very hard to estimate, as although the onset can generally be sharply defined, recovery is usually much more gradual.

About three years was the average duration of the illness in these cases. A similar period has been given from a study of the cases at the Mayo clinic, and

it has been suggested that the illness is more acute during the first nine months. This series also agrees with that view, and cases are more likely to end fatally during the first year than at any other time.

During the course of the disease waves of improvement and relapse are usual, but when there has once been sufficient improvement for a return to normal life, relapse is uncommon.

Aetiology.

Sex. The disease is much more common in women. In these cases the proportion is 17 to 1.

Age. The age distribution of these cases (excluding those diagnosed hyperthyroidism following a parenthymatous goitre) was: 10–14, 2; 15–18, 18; 19–22, 26; 23–26, 13; 27–30, 20; 31–34, 9; 35–38, 3; 39–42, 5; 43–46, 4; 47–50, 2; over 50, 3.

True exophthalmic goitre is very rare before puberty; it is increasingly common from 14 to 24; still common from 25 to 34; relatively uncommon from 35 to 44; and much rarer after this age, which may be taken roughly as corresponding with the menopause.

Most attacks occurring after the menopause are much less severe in their signs and in their duration than ordinary cases.

Of the small number classed as hyperthyroidism following a parenchymatous goitre, the average age at the onset of symptoms was 37, and the average age at the onset of the goitre was 22 years. Plummer (2), in an analysis of the cases from the Mayo clinic, gives very similar figures, 36 and 22. The age distribution is therefore another factor distinguishing these two groups.

Marriage. In reading through this series of cases typical cases of exophthalmic goitre seemed relatively rare among married women, and especially among those with more than one child. Such an impression is difficult to verify statistically, especially when the average early age of onset is taken into account. In this series there were twenty-six married women only among 102 cases of true exophthalmic goitre. The results are shown in Table I.

TABLE I.

1. Age	Below 20	21–24	25–28	29–32	33–36	37–40	Above 40
2. (*a*) Married	0	3	8	12	10	8	16
(*b*) Not married	49	30	24	17	14	4	3
3. Probable number of cases among unmarried women	—	7·8	6·8	5·3	3·1	2·2	3·7
4. Ratio $\frac{2b}{3}$	—	3·8	3·5	3·2	4·5	1·2	

In row 2 are shown the number of married and unmarried women at different ages in this series of cases, and in Hale-White's series. Row 3 gives the probable number of cases among unmarried women, if they suffered from exophthalmic goitre in the same proportion as married women; and row 4 the

ratio of this figure to the actual number of cases which occurred. The number of unmarried women among the general population for each ten married women was found from the census reports (3).

At all ages up to 36 exophthalmic goitre is three or four times as common among unmarried as among married women. No doubt some of this difference can be explained by the fact that married women with children are less ready to come into hospital for treatment, but it could hardly account for such a large difference. After 36 the relative incidence is almost the same as would be expected from the number of married and unmarried women in the general population. These conclusions have been confirmed by another series of cases which Mr. Romanis has kindly sent me of patients who have had thyroidectomy for Graves's disease.

There are two possible conclusions. Exophthalmic goitre is more likely to occur among unmarried than among married women. Or women who later develop exophthalmic goitre are abnormal in some way before they develop any obvious signs of the disease, and this makes them less likely to get married.

Pregnancy. From these general results it seemed worth while to examine rather more closely the effects of pregnancy on the disease.

Among the cases of true exophthalmic goitre there were twenty-six married women. Ten of these were over 40; among these there were families of the normal size, and the disease occurred when the normal period of child-bearing was over, or almost over. Sixteen of the married women were under 40. These had had twenty-four children, an average of 1·5.

There is no mention in this series, or in the series published by Hale-White, of any case who was made worse by a subsequent pregnancy. There are several cases where improvement was attributed to pregnancy, and it seems probable that this has a real influence, and that it is not merely due to coincidence.

Family History. As regards mental disorder the results are of little value, but the parents of two cases were in an asylum, and one had committed suicide.

The family history of exophthalmic goitre is much more common. The mothers of two cases had suffered from it, the sisters of four cases, and first cousins of two cases.

As probably not more than one person in ten thousand suffer from this disease, this correlation is high enough to prove the inheritance of a liability to Graves's disease, and low enough to disprove any direct inheritance, even were this probable on other grounds.

There is no evidence that exophthalmic goitre was associated with a family history of parenchymatous goitre, apart from those cases in whom symptoms of hyperthyroidism developed many years after an ordinary goitre. In other respects, also, the family history appeared normal.

Previous diseases. Rheumatic fever shows a slightly higher incidence, but chorea and mitral stenosis show a much higher incidence, among these cases of exophthalmic goitre than among other general admissions to the medical wards.

The correlation with chorea is specially interesting, as this too is more

likely to attack girls than boys, and more likely to attack the emotional than the normal stable child.

Diphtheria and tonsillitis show a much higher incidence in the cases of exophthalmic goitre than elsewhere. At first this seems to support the view that the disease generally follows from primary infections in the neighbourhood of the throat. But a closer examination only shows six cases where the disease seemed to follow closely on the infection. Case 124 is the most striking of these; here there were certainly severe and repeated attacks of tonsillitis and the signs and symptoms cleared up after tonsillectomy. But this was quite unusual. There was also one case where exophthalmic goitre and rheumatic fever developed simultaneously.

Much more striking are the number who developed acute infections while they were actually in hospital for Graves's disease. Seven cases had attacks of tonsillitis sufficiently severe for swabs to be examined for diphtheria. One developed diphtheria, one typhoid, one scarlet fever, two rheumatic fever, and two chorea.

The resistance to disease is evidently much lowered in patients with exophthalmic goitre, and this no doubt explains the special liability of such patients to death from pneumonia after anaesthetics.

It has also been suggested that chronic infections, such as septic tonsils and pyorrhoea alveolaris, play an important point in the pathology of exophthalmic goitre. These cases do not lend support to this view.

Prognosis.

During these ten years there were 127 cases. 89 of these, or over 70 per cent., were traced, and 30 were again examined at hospital.

Of these eighty-nine, eight died in hospital of exophthalmic goitre, or of terminal infections such as pneumonia, while they were still acutely ill, and one died with carcinoma of the pancreas.

Of the eighty who were traced after they were discharged from hospital, seven died of exophthalmic goitre, and five of other diseases—acute appendicitis, perforated gastric ulcer, pneumonia during the influenza epidemic, and two of heart disease of many years' standing, probably independent of the hyperthyroidism.

In deciding on the general prognosis, some account must be taken of the cases who could not be traced; otherwise the more severe cases who died early in hospital would make the prognosis unduly grave. The cases lost sight of were mostly in hospital during the early years 1908–10.

There is no reason to suppose that the cases before 1910 were different from those after; it is fairest to assume that the relative results among the thirty-eight, who could not be traced, were the same as among the eighty who could be traced.

Hale-White's figures have sometimes been criticized because of the large proportion who could not be traced. It has been suggested that many of these had

died. But his cases went back for twenty years, and would naturally be very difficult to trace. The most prompt replies to my inquiries were generally from the relatives of those who had died; and this makes it unlikely that the majority of the untraced had died. A young woman who recovers and gets married is quite as likely to be lost sight of.

It is difficult to know how far the prognosis for those who were sufficiently ill to come to a general hospital can be taken as a true prognosis for the disease as a whole. Probably, with an illness of such long duration, most patients are seen by a consultant or by a general hospital.

Hale-White found that cases who were classified as severe did rather better than those who were classified as slight cases. For these reasons the prognosis of this series may be taken as fairly representative of the prognosis of exophthalmic goitre in general.

I have divided all the cases into five groups.

Group I includes those who were completely cured; i.e. those who complained of no symptom of ill health, and showed no sign of Graves's disease on examination. This group consists of seven cases, five of whom had had severe attacks.

Group II includes those who were almost cured; i.e. those who were able to lead a normal life, earning their own living if necessary, but still showed, to a slight extent, one or sometimes two signs of Graves's disease. This group consists of 26 cases.

Group III includes those who were much improved; i.e. those who were able to do light work, or actually earn their living by light work, but still showed marked signs of the disease. This group consists of 29 cases.

Group IV includes those who were not much, or not at all, improved, and consists of 11 cases.

Group V includes those who died of Graves's disease, and consists of eight who died in hospital, and seven who died afterwards.

These results are shown in Table II.

TABLE II.

	Died in Hospital.	Cases traced (80).	Not traced (38).	Total.	Percentage.
I. Cured	—	7	3	10	8
II. Almost cured	—	26	13	39	30
III. Much improved	—	29	14	43	34
IV. Not improved	—	11	5	16	13
V. Died	8	7	3	18	15

Of the twelve cases of hyperthyroidism supervening on a parenchymatous goitre, one died some years later of what may have been uraemia. Five were cured and six were improved, so that the prognosis is relatively good.

Hale-White expressed his results rather differently, so that direct comparison is not possible. 21 of his 169 died in hospital. Of the 54 who were traced 8 had died.

Calculating his results by the same method as I have adopted, and expressing the results as percentages in the same way as in Table II, 57 per cent. had done well; 21 per cent. were moderately well; 4 per cent. were not better; and 18 per cent. died.

Some of the cases in his first group who had 'done well' would not have been included in my group as 'almost cured'. Some who were in the second group as 'moderately well' would have been included in my Group IV as 'not very much improved'.

This shows the difficulty of comparing conclusions, unless an exact definition of recovery and improvement has been agreed on by the different observers.

The two series are sufficientlv concordant to prove that the results are good in from 40 to 60 per cent.; moderately good in from 20 to 30 per cent.; unsatisfactory in from 5 to 15 per cent.; and that the mortality is rather under 20 per cent.

These are not the results which can be expected after a few months of medical treatment, but after, on an average, three years with long periods of rest and medical treatment.

They cannot be regarded as ideal results. Most patients would gladly submit to the risk and inconvenience of operation, if a better prospect of recovery could be promised with reasonable certainty.

It seemed worth while to compare, under strict conditions, a series where some were treated medically and some surgically.

In considering the relative results of these treatments there is no need to make any assumption about those who could not be traced. I have excluded the five cases who died within a year—sometimes within a few months—of the onset of their illness, because I do not think most surgeons would have operated on these cases. I have also excluded two cases who died after operation, as my object is to discover the permanence of the improvement after thyroidectomy.

The results are shown in Table III.

TABLE III.

		After Partial Thyroidectomy (16 cases). %	After Medical Treatment (56 cases). %
I and II.	Cured or almost cured	38	41
III.	Much improved	38	28
IV.	Not improved	12	17
V.	Died	12	14*

* This figure would be raised to 21 per cent. with corresponding reductions in the other figures, if the five early deaths are included. The figure is too high for the reasons given.

The results are too few for one to be able to draw any definite conclusions; but they show that the results of partial thyroidectomy are not always so much better, that one ought to neglect the possible danger of an operation and advise it on every occasion.

I do not know of any other results where a strict comparison can be made,

as in these cases. The immediate result of operation is generally an enormous improvement in all the symptoms, but it is much more difficult to know what are the final results. Certainly relapse is not rare after an operation, and on general physiological principles might be expected.

But if the disease has a natural tendency to recovery, an operation may just prevent permanent damage to the heart, or other systems, by the hyperthyroidism.

The most satisfactory results of surgical treatment, which have been published in England, are those of Berry (4).

He gives the following results on 78 cases: Almost cured, 53, or 70 per cent.; better, 18; no change, 4; died, 3.

The results are very similar to those given in Hale-White's series, except for the striking difference in the mortality. Unless the cases are taken under strictly comparable conditions, it is difficult to know how much of this can be attributed to the result of thyroidectomy.

Klose has collected the results of thyroidectomy in 1,126 cases, where the operation was performed by twenty-six different surgeons. The average result was 60 per cent. cured—a figure which is not greatly superior to the results obtained by medical treatment.

Unfortunately, it was not possible from these cases to test the value of X-ray treatment. Some of the most complete cures have received this treatment, some recovered without. Those who received X-ray treatment in hospital did not appear to recover more rapidly than some others who were treated with rest and medicine. In some cases the signs and symptoms persisted after long periods of this treatment.

Distribution in England and Wales.

I have tried to discover if exophthalmic goitre was more prevalent in some areas than others, in view of the known facts with regard to endemic goitre, and some possible connexion between the two.

The most reliable data are the deaths which are returned as due to exophthalmic goitre—information which was kindly supplied to me by the Registrar-General for the seven years 1913–19. They were summarized in four groups—London, county boroughs, urban districts, and rural districts. The results are shown in Table IV.

TABLE IV.

	Deaths from Exophth. Goitre Yearly.	Total Deaths (5).	Population in Millions (5)	Ratio Column 2 / Column 1.	Ratio Column 1 / Column 3.
London	38	59,000	4·4	1,560	8·6
County boroughs	135	176,000	12·1	1,300	10·9
Urban districts	157	160,000	12·3	1,020	12·8
Rural districts	118	99,000	7·2	840	16·4
Total, England and Wales	448	494,000	36·0	1,100	12·2

Column 4 gives the number of deaths from other causes for each death from exophthalmic goitre; and column 5 the number of deaths from exophthalmic goitre for each million of the population living.

By whichever standard we judge, deaths from exophthalmic goitre are least common in London, more common in most other large towns, still more common in the small country towns, and most common in the country. Probably this represents a real difference in incidence and not merely in fatality. Exophthalmic goitre is nearly twice as common in the country districts as in London.

Owing to this difference, it is not possible to compare directly all the cases in one area; because a densely populated area would show too low a mortality. If the rural districts and urban districts of each county are taken separately, there is a general agreement between the death-rate in each. This suggests that seven years is a sufficiently long period to give reliable results.

TABLE V.

The number of deaths from exophthalmic goitre of each million of population living.

(The figures for some towns are given in brackets.)

South Western Counties (Devon, Dorset, Cornwall, and Somerset)	20
(Plymouth 20)	
South Eastern Counties (Surrey, Sussex, Kent, and Hampshire)	13
South Midlands	11
Excluding Middlesex and Hertford	13
Middlesex and Hertford	9
(London 8·6)	
Eastern Counties (Lincoln, Norfolk, Suffolk, and Essex)	13
Excluding Essex	16
Essex	7
North Midlands	13
(Birmingham 10)	
Wales	14
Excluding Glamorgan and Monmouthshire	21
Glamorgan and Monmouthshire	9
(Cardiff, Swansea, and Merthyr Tydfil 11)	
Northern Counties (with Yorks., Lancs., and Cheshire)	16
(Manchester and towns of Lancashire 14)	
Excluding Durham	17
Durham	9
(Newcastle, South Shields, Sunderland, Gateshead, and Tynemouth 8)	

In general, the death-rate in the towns agrees with the surrounding country area; where there is a high death-rate in the country, there is a relatively high death-rate in the towns. The most striking fact is the high incidence in the west—in Devon and Cornwall, in Wales, and in Cumberland and Westmorland.

The lowest incidence is in Essex, Hertford, Middlesex, and London—a block on the north side of the mouth of the Thames. Durham and Monmouth show an almost equally low incidence, but it is not so certain that seven years is a long enough period to give reliable figures for small areas. The same criticism applies to Oxford, though the incidence is equally high for the city, for the urban, and for the rural districts, which suggests that it has some real meaning.

The Midlands, as a whole, show a rather low incidence, but not as low as Essex and the neighbouring counties. Even apart from the frequency on the west coast, there are more cases round the coast than inland.

It would be dangerous from these seven years to draw conclusions about the aetiology of Graves's disease. In general, the areas with a high incidence are the mountainous areas with the old Celtic population. The three areas with a specially low incidence are all round large industrial areas—London, Newcastle-on-Tyne, and the mining towns of South Wales. But Birmingham and Manchester do not show the same low incidence, and seem to agree with the surrounding country areas. It would be very interesting to compare these results with the facts in other countries.

Unfortunately, I have not been able to find any reliable information about the distribution of ordinary goitre in England. Derbyshire is notorious for the prevalence of endemic goitre, but exophthalmic goitre does not seem to be common. The close association of cretinism with endemic goitre makes it unlikely that there would also be a close association with Graves's disease.

Discussion.

There has been much discussion about the nomenclature for exact cases which should be included as exophthalmic goitre. Plummer (2) has differentiated very clearly between two groups. In one the signs and symptoms arise suddenly; in the other, a goitre which has given rise to no symptoms changes in some way, and begins to give rise to symptoms. The justification for this division, which has, no doubt, been recognized in practice for many years, lies in the other clinical differences which are found in these groups.

The classical descriptions of exophthalmic goitre (Graves's disease, Basedow's disease) agree with the former group, and it is a clearly defined condition. In all cases the majority of the following signs and symptoms are found, and have developed within a short period—exophthalmos, enlarged thyroid, tremor, tachycardia (above 100), increased metabolism, increased sweating, and undue nervous excitability. At least five of these signs are present in almost every case.

In the latter group, where a goitre has preceded the onset of symptoms by some years, the clinical picture is different. Exophthalmos is much less common, and often less noticeable even when present; and generally only two or three of the other cardinal signs and symptoms are present.

As a rule the patient is not nearly so ill, and the mortality is relatively unimportant. Perhaps the term hyperthyroidism might be used more generally for these cases. They resemble much more closely cases where toxic symptoms develop after an adenoma, and can be cured by its removal. No doubt, the underlying pathology of the two conditions is the same, and this means that

there will be cases intermediate between the two groups. But clinically the distinction is valuable, because cases generally belong clearly to one group or the other. Although hyperthyroidism, so defined, does not tend to develop into true exophthalmic goitre, there is a stage in the recovery of the latter, when only a few of the symptoms are present, and the diagnosis might be in doubt without the previous history.

Some of the cases occurring among middle-aged and elderly women, where the mental changes are well marked and the physical changes rather slight, belong really to this group, although the thyroid enlarges at the same time as the onset of the illness and not before.

If Plummer's definition is changed to include these cases also, the distinction becomes of even greater clinical value.

It is only in a small percentage that the onset of the disease can be attributed to any one definite factor. Sometimes inheritance, sometimes infection, and sometimes a severe mental shock appears to be the important factor; but no one of these seems to be operative in more than 10 per cent. of the cases. The underlying pathology must be something different, and must be very similar in all these cases. It appears to be a disturbance of the endocrine balance in the body—hyperthyroidism being the most striking feature.

In practically all fatal cases, and probably in most others, the thymus is enlarged. In spite of the claims which have been put forward for the thymus, and the reported improvement after its removal, or treatment with X-rays, it is not probable that the changes in this gland are in any way primary.

Associated with this enlargement of the thymus is a relative lymphocytosis. Anaemia has often been stated to be associated with Graves's disease. But blood-counts in hundreds of cases of Kocher's, and of the Mayos', have shown conclusively that the haemoglobin percentage and red cell count are within normal limits. The white count is generally normal, but sometimes slightly diminished. The relative lymphocytosis is the only constant change.

Of all the cases of exophthalmic goitre in this series 87 per cent. were in women of child-bearing age, and 67 per cent. in unmarried women of child-bearing age. Nothing is known of any difference in the histology of the thyroid in men and women, or in the chemical properties of its active principle. There are many facts pointing to a special relationship between the thyroid and the ovary. Enlargement of the thyroid occurs most commonly at puberty. The thyroid has been found to be enlarged in 50 per cent. of cases of pregnancy by Ripman and by Van Graaf (6). In some women it enlarges regularly during menstruation. On the other hand, myxoedema occurs most commonly at the menopause.

But one must remember that cases of exophthalmic goitre—typical in every respect—do occur in men, in women after the ovaries have lost their function, and more rarely in children before puberty.

The facts are sufficient to show that hyperthyroidism is much more readily

produced during the period of life when the ovary is functionally active; but that the cyclical physiological changes of pregnancy are in some way antagonistic to the development of Graves's disease.

Conclusions.

1. Exophthalmic goitre is a clearly defined condition, in which the majority of the following signs are all present within a short time of the onset of the disease—exophthalmos, enlarged thyroid, tremor, tachycardia (over 100), increased metabolism, increased sweating, and undue nervous excitability. Amenorrhoea is frequently present. More severe mental changes and bouts of pyrexia and diarrhoea are characters of the disease, but are not so constantly present.

2. Hyperthyroidism is suggested as a convenient term for a much less marked condition, in which two or three only of these signs are present. It is less dangerous and more easily cured. It does not tend to develop into true exophthalmic goitre. It occurs generally in older women; often a goitre has been present for many years without giving rise to any symptoms.

3. Exophthalmic goitre is four times more common among unmarried than among married women—even after making allowance for the age incidence of the disease. Nearly 70 per cent. of all cases occur in unmarried women of child-bearing age.

4. The signs and symptoms of exophthalmic goitre are, in the main, those of over-secretion of normal thyroid substance. There is some evidence that associated with this there are changes in the internal secretion of the ovary and other glands.

5. During an attack of exophthalmic goitre the resistance to infection is very much diminished.

6. Taking round figures the prognosis for exophthalmic goitre is as follows: Almost cured, 40 per cent.; very much improved, 30 per cent. (all these 70 per cent. are able to return to a normal way of life, or at least perform a fair amount of work without inconvenience); not much improved or worse, 15 per cent.; died, 15 per cent. The average duration of the illness is about three years. In most of the fatal cases death takes place within the first year.

7. As a result of thyroidectomy, there is in most cases great immediate improvement. One cannot yet be certain that the final result is greatly superior to that obtained by medical treatment. But even after allowing for the operative mortality, which in skilled hands can be reduced well below 5 per cent., there appears to be a much smaller proportion of fatal cases. Where a long period of rest is not possible, cases may be saved from permanent damage to the heart by operation. In all cases the period of rest can be much reduced.

8. Exophthalmic goitre in England is more common in the country than

in the towns, more common in the west than in the east, and more common on the sea-coast than inland. It does not appear to be specially prevalent in areas where goitre is endemic.

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CRITICAL REVIEW

THE RESULTS OF GONORRHOEAL INFECTION OF THE NERVOUS SYSTEM

By E. O'CONNOR

Introduction.

Of infections we know that many are mainly local, others generalized; and of the latter many or most have their special affinity for special structures, while others, often the most virulent, attack with impartial destructiveness every part of the human organism.

Less generally, infections may fail to conform to type, owing to the idiosyncrasy or lessened resistance of their victim, or to neglect of treatment, traumatic accidents, or unknown causes. Thus an infected scratch may develop a fatal septicopyaemia within a few hours; or, conversely, a systemic infection, such as syphilis, may rarely almost confine its appreciable manifestations to the primary lesion. Thus infectious diseases have their most probable complications and their rarer sequelae.

Unless then we are prepared to deny that gonorrhoea, commencing as a local infection, may assume the rôle of a general infectious disease, we shall be prepared for the possibility of gonococcal nervous complications; and ample quotations will be submitted from the experience of clinicians in confirmation of this development.

The general method followed in these pages is, in the first place, a rough classification of the parts of the nervous system mainly affected, and in each of these sections a preliminary collection of the opinions found in the literature, mentioning cases to which they have reference.

One or two cases appearing recently in an important London venereal clinic have been included and the records of the hospital searched for any light that might be thrown upon the subject. The result of this search has been meagre, as was to be expected in the case of such rare complications.

We are not in a position to determine whether the nervous system is usually invaded through the lymph channels or the blood, nor even in which cases the gonococcus and its toxin are respectively responsible.

There will be found some scanty evidence of the presence of the micro-

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organism in the involved nervous regions; but there is nothing to show that the toxin alone is incapable, in other instances, of producing similar effects. It is also extremely probable that many are due to a mixed infection, as indeed the primary urethritis often is. But we may accept MacDonagh's view that the rare cases of involvement of the central nervous and cerebro-spinal systems in gonorrhoea are in the main metastases.

It must be borne in mind that a definite scientific classification is impossible where, in the first place, the very existence of such an origin of nervous disease is by no means universally admitted; and where, in the second place, the symptoms very often indicate overlapping of the portions of the nervous system involved, and have not been finally allocated by post-mortem examinations.

Psychopathy.

The psychologic type most commonly met with in gonorrhoea is exemplified by neurasthenia and hypochondria; but the disease may take on a generally infectious character, leading to cutaneous, spinal, or cerebral complications.

Tanton quotes Burque as having found gonococci in the blood in cases of gonorrhoea showing no symptomatic complications; though the latter expressly states that we must not conclude that this happens in all cases: still that, if not always, very frequently gonorrhoea is complicated by septicaemia. Ward, on the other hand, when referring to the fact that gonorrhoeal metastases are rarer than generalized toxaemia, goes so far as to add that in fact the latter is constant, though seldom serious; and it seems only reasonable to expect that where there is a local bacterial infection in any part of the body, some toxic elements must necessarily get into the blood, in however dilute a form. On this hypothesis we may perhaps account for the invariable symptom of mental depression accompanying gonorrhoea and other occasional gonorrhoeal psychoses. Similar phenomena appear in other local infections.

Venturi's *pyophrénie*, for which he quotes the analogy of puerperal mania, attributed by many authorities to an infectious origin, is perhaps only another name for the same thing: but he does not exclude a specific gonorrhoeal *folie*. He also suggests as the morbid anatomy a serous effusion in the subarachnoid space, comparable to that in the knee-joint in gonorrhoeal arthritis.

Delamare includes, as *délires fugaces*, cases of Tixier, Bourdon, Meuriot, Vidart, Bonnet, and d'Amaral, the last case being a delirium followed by a semi-comatose state, and all accompanied by gonorrhoeal arthritis: he adds to these six cases of Venturi. The only post-mortem showed cerebral anaemia. Venturi suggests that probably the cases are examples of insanity accidentally provoked in degenerates or alcoholics by gonorrhoea. In other toxic insanities we know, on the authority of Stoddart, that there is sometimes found oedema of the pia-arachnoid, with possible diapedesis of the leucocytes in the perivascular spaces.

Cascella mentions a patient aged 24, himself somewhat irritable and unstable, and the son of an alcoholic father, whose equilibrium was upset by an attack of gonorrhoea contracted in Naples. The mental symptoms were melancholy and confusion of ideas, together with apathy and suicidal tendencies. He was sent to an asylum, but recovered with the cure of the gonorrhoea; reinfection with gonorrhoea brought a return of the psychopathy. Altogether he appears to have recovered four times from the mental condition, but finally developed furious mania and was lost sight of. Cascella refers to Venturi's phrases, 'blenorrhagic psychopathy' and 'pyophrénie'. Here was hereditary mental instability, ready for collapse on the approach of mischief; and there seems to be no sound reason for rejecting the evidence that the gonococcus proved itself eminently capable of providing it.

Wooten reports on a perfectly healthy man of 36 years of age, without any history of tuberculosis, syphilis, nephritis, or trauma, who had a train of nervous symptoms, which will come under notice later, following gonorrhoea, and in the course of the illness developed restlessness aggravated to the point of acute mania; and towards the end muttering delirium.

Luys mentions a case of Bieck's, a man of 48 years of age, with a year's urethral discharge, who developed a fresh gonorrhoea followed in less than a week by delirium and mania, then coma and death. Exudative patches were found on the cerebral pia mater, especially of the right frontal and parietal convolutions; while gonococci were found microscopically.

Batut mentions a case of hysterical coxalgia at Lyon in 1907, with all the symptoms of coxo-femoral arthritis, accompanying the first gonorrhoea of a young soldier.

Chavrier and Février's case of a healthy trooper of 22 years of age, attacked, a fortnight after a gonorrhoeal urethritis (cured in a week!), by nervous symptoms including choreic movements of the right shoulder, and flexion of the head on the same side, may suggest hysterical chorea, rejected by the authors owing to the absence of hemianaesthesia, restriction of the visual field, and other features.

Glynn rejects a hysterical basis for his case of gonorrhoeal pseudo-tabes and polyneuritis on the ground that the sensation was no more affected in the paralysed limb than elsewhere.

Aronstamm states that neurasthenia and psychic disease are liable to follow in the wake of genito-urinary disorders, alluding to the theory of an absorption of virus from the genito-urinary tract, which reacts upon the nervous system; and that the true predisposing cause is nervous instability. He describes three cases of cured gonorrhoea, the patients suffering from a psychic conviction of the persistence of the disease, one of them being transformed from a manly individual to a hang-dog nervous wreck threatening suicide.

Famenne of Brussels reports on three cases of normal individuals, without family history, who after acute gonorrhoea developed 'systematized insanity of persecution', and theorizes to the effect that the infection created in the patients a predisposition analogous to hereditary predisposition; and acted by massive

diffusion of toxin throughout the organism, or more likely by the 'perturbation caused in the genital secretion': the nature of the insanity being in relation to the nature of the infection in such cases, mental confusion in influenza, neurasthenia in tuberculosis, hypochondria in syphilis, hallucinations and troubles of the imagination in alcoholism. Though it may well be that the clinical picture is affected by the nature of a toxin, it would appear to be rather dangerous to insist upon too much specificity without the experience of a very large number of cases.

Sexual impotence occurring as a result of gonorrhoea is much more likely to have an anatomical than a psychic basis, although the former may escape detection; but a transitory impotence of psychic origin is so frequent as not to require to be established by special cases. Neurasthenia, hypochondriasis, melancholia, or mental depression are too well established by experience of patients with obstinate gleet to need any individual evidence. It seems most reasonable to attribute such manifestations to a slight toxaemia; although in some cases the so-called neuroses referred to by Jullien may be, as he says, attributable to the moral side; but his refusal to accredit any such phenomena to the gonorrhoeal poison may be said to be out of date.

Central Nervous System.

Moltschanoff reported the result of inoculating twenty-five guinea-pigs and twenty rabbits with gonotoxin. The cells of the cerebral cortex were found to have suffered, though in less degree than the spinal ganglia cells; and this applies to the large ganglia and nuclei of the cerebral nerves: there was also some hyperaemia of the cerebral membranes. If therefore we can draw any conclusion from such experiments as to the action of the toxin on the human organism, we should be prepared to expect the gonotoxin to affect the central nervous system.

Fournier mentions among the complications of gonorrhoea a temporary diplopia (some forms of which can be regarded as a nervous lesion) and partial deafness; both accompanying a multiple arthritis, the eye symptoms usually coinciding with the arthritic. The aetiology is dominated by gleet and idiosyncrasy.

Glynn states that cerebral symptoms such as hemiplegia and aphasia due to embolism may develop. Raymond considered that meningitis was the only possible cerebral complication of gonorrhoea; but refused to accept Bonnet's theory, attributing the nervous symptoms to arthritis. Pitre refers to papers of Tambourer and two cases. The first, a man of fifty-nine years of age, had acute gonorrhoea with arthritis in 1886, followed by sudden right hemiplegia with aphasia. Two months later he had ten attacks of Jacksonian epilepsy, with a fatal result. *Post mortem* there was softening of the Sylvian area, the middle third of the first frontal convolution, and the posterior quarter of the ascending parietal and insula, and nearly all of both first temporals. There was no arterial atheroma. The heart was healthy, but there was a right renal abscess. Pitre

concludes that if further cases should occur, the theory of cause and effect between the hemiplegia and gonorrhoea might have to be considered; there would be nothing surprising if the brain does not always escape, gonorrhoeal myelitis being already known. The patient's previous medical history would be appreciated; but as the case stands it may be accepted as provisional evidence of a gonorrhoeal hemiplegia.

The second case was a soldier 24 years of age: first gonorrhoea 1883; cured in fifteen days by copaiba and zinc sulphate: second attack in 1885 of five weeks' duration. This was not quite cured when the patient had sudden vertigo one morning on rising, followed by left hemiplegia. In a few weeks he could walk fairly. Examined in June, 1886, he still had slight facial asymmetry and slight want of co-ordination of the movements of the left hand; the left knee-jerks were exaggerated; there was epileptiform tremor on raising smartly the point of the left knee: no atrophy or urinary trouble or atheroma of peripheral arteries. Tambourer himself attributed the embolism to gonorrhoea, a diagnosis which Delamare said would have to be tested by time. The criticism expresses fairly the caution necessary in accepting a novel phenomenon; but the coincidence and the absence of any ascertained cause for the hemiplegia, other than the gonorrhoea, are impressive. Still, the family history and previous medical history of the patient would have been relevant to the report.

Recently a case appeared in MacDonagh's Clinic at the Dean Street Hospital, London. The patient was a man of thirty-eight years of age, who had gonorrhoea seventeen years ago, which for a month was neglected, though severe in type, until orchitis compelled the patient to seek advice. There was a second attack of gonorrhoea sixteen years ago, lasting two or three months. The patient admits that he had a small pimple on the penis a week after exposure to infection, but it disappeared within ten days; and he also had somewhat swollen inguinal glands, which, however, were tender. He is perfectly frank about his symptoms, and declares that otherwise he 'never had a spot on his body', and any suspicion that these appearances were syphilitic may probably be safely dismissed. A third attack of gonorrhoea occurred fifteen years ago, lasting a couple of months. He admits having neglected every one of these attacks. Fourteen years ago he had right iritis, diagnosed as syphilitic by an Italian physician. A fortnight later patient awoke to find his right arm paralysed, face contorted, impediment in speech. At that time he had no gleet. He was actually treated for syphilis by six or seven mercuric injections. Three years later an iridectomy was performed in Brussels. Some time afterwards he had another paralytic attack. A Wassermann was negative. Nevertheless it was considered better to treat him with '606', and he had a full course, together with mercuric injections. He states that six or seven blood tests were done and all negative. After all he got a third attack of paralysis, losing this time the use of the right leg as well as arm, awakening in the morning with sharp pain at the 'top of the neck as if stabbed'. He recovered again in three or four months, and was well until August, 1919, when a fourth attack deprived him of the use of his right arm and leg and feet. He

then spent three months in a London hospital and had two more negative Wassermann reactions, as well as a lumbar puncture. Afterwards he went to a convalescent home for three months, and has done no work since, having become somewhat obsessed with the fear of another attack, and in consequence attended for treatment, as well as on account of a fresh attack of iritis occurring about a fortnight before he came to hospital. He has had 'rheumatic pains' in both knees, and sometimes in the right upper arm, 'like a vice'; also occasionally 'pins and needles'. When examined, patient complained of some general malaise. The grip of the right hand and the muscular power of the right hand and right arm were good, though slightly weaker than the left. He complains of some 'wobbling' in his gait when tired. He could not rise well on the toes of either foot, especially the right; had a slight tendency to sway with the eyes closed; but attributed this, not to vertigo, but to weakness of the right leg. He states that he is strictly temperate, and has never been drunk in his life. He says that gonococci were recently found in his urine in a London hospital. The right knee-jerk is somewhat more active than the left, but both approximately normal; elbow-jerk brisk in the right arm, present in the left; left nasal furrow rather ill-defined; right side of prostate somewhat swollen and tender; some urgency of micturition; no epitrochlear or posterior cervical or inguinal or other glands now palpable; arteries normal to palpation; pulse 84; and heart-sounds appear normal except possibly for a trifling blurring of the mitral first sound. I elicited nothing in the family history, except that the father had been in an asylum. The patient was doing well at the time of examination and for a few weeks afterwards. This case is at least suggestive; and may be taken as some confirmation of Tambourer's diagnosis in regard to his soldier patient.

Delamare quotes cases of Panas, d'Heberth (or Hilbert), Cros, Fromaget, and Fischel. Both he and Tanton refer to two cases of Panas, to which they assign different dates. Both were gonorrhoeal optic neuritis. Delamare describes one as 'double sciatica without iritis; both eyes papillo-retinitis; right amblyopia. Visual field restricted; scotoma.' Tanton describes one case as 'sudden unilateral abolition of vision; oedematous papilla; tortuous and dilated veins; filiform arteries'.

Kienboch mentions Welander's patient whose facial and recurrent laryngeal nerves were involved in a polyneuritis. Also Fischer for deafness and Panas for atrophy, and Lazarus for paralysis of the vocal cord.

Batut summarizes cases of 'sensorial neuritis', quoting Panas's case of a male with generalized gonorrhoeal arthritis, in which sudden blindness of the right eye supervened, and troubles of the left vision due to optic neuritis, from gonococcal involvement of the second nerve; the case of Cros, sudden optic neuritis; Fromaget's case of urethritis with iritis, without gonorrhoeal conjunctivitis; 'undeniable symptoms of optic neuritis'; Basile's, with right optic neuritis and neuritis of the third nerve due to gonorrhoeal infection, in the course of which gonococci were found, though they had disappeared from the urethra; also left ptosis, and slight convergent strabismus with amblyopia, and temporal hemi-

anopsia. The patient improved. Also Fischel's, gonorrhoea with persistent auditory trouble, attributed to the direct action of the gonococcus on the termination of the eighth nerve. There was no middle ear suppuration or other possible cause. Lustgarten considered the case neuritis, Fischel as vaso-motor or trophic and reflex genital irritation. Also d'Heberth's, gonorrhoeal double labyrinthitis with extreme rachialgia and vertigo in a patient with urethritis; almost complete unilateral deafness: the vertigo was cured by lumbar puncture and pilocarpine, but the deafness persisted. Also Martino's male patient in the fourth month of a gonorrhoeal discharge, who suffered successively in each ear from deafness, attributed to gonorrhoeal acoustic neuritis in the absence of other cause. There was gradual improvement under antigonococcal treatment.

Gowers mentions a man of twenty-two years of age, with gonorrhoea before admission to hospital and a discharge lasting a fortnight, who had slight frontal headache a week before admission, with mistiness of vision, and four days later was unable to see to work, from neuro-retinitis. There was no history of alcoholism. There was considerable oedema at the edges of the disks of both fundi; a white line along the vessels, slight evidence of old neuritis in one eye, slight inguinal and axillary adenitis; difficulty in turning the eyes upwards. He inferred that the gonococci were deposited on the optic chiasma. There was a large scotoma in the central part of the field, suggesting retro-ocular neuritis. Inflammation spread to the retina. Marshall refers to this case and remarks that Wassermann was negative.

These cases cannot all be lightly dismissed. Each by itself could establish no proved connexion between the venereal disease and the cerebral lesions; but the cumulative effect is a fairly strong impression of such a relationship. It must, however, be admitted that more detailed and exclusive evidence would be welcome in some of the reports.

Cerebro-spinal Meningitis.

Raymond and Cestan assert that true gonorrhoeal metastases occur, and that numerous cases of encephalic or cord changes have been imputed to the gonococcus. Ricord has seen, in association with gonorrhoeal arthritis, symptoms of cerebro-spinal compression, which seemed to vary with the extent of the joint effusion. Delamare, however, comments on the almost complete absence of anatomical confirmation of the cerebro-meningeal manifestations, if such exist, of gonorrhoea. Batut states that they are very rare, and that many cases of meningitis occurring in the course of that disease are independent of it. Koch rejects de Jong's case of gonorrhoeal meningitis on the ground that the bacterial findings were not convincing: e.g. there was no agglutinin test, nor even sugar test. He accepts Weichselbaum's dictum that no case of gonorrhoeal meningitis has been 'demonstrated in peremptory fashion'. On the other hand, he accepts the case of Henderson and Richie as establishing that in this instance the

'meningitis appears to have been clearly the work of the gonococcus'; the laboratory technique naturally appealing to him.

Allbutt and Rolleston, however, accept de Jong's case, remarking that he 'seems to have definitely established the gonococcus as causal agent'. Rawls asserts that the gonococcus has been found in the fourth ventricle of the brain. MacDonagh states that gonorrhoeal involvement of the central nervous system is very rare; that there is no proof that it is due to the gonococcus: it may be due to the gonotoxin; but there is a presumption in favour of the former, because the infection behaves like a metastasis.

Kienboch refers to Fürbringer's case as an example in which only an accidental connexion with gonorrhoea may be assumed. He adds that the diagnosis often cannot be made in the absence of any post-mortem examination and bacterial investigation; and that even a probable diagnosis of purely cerebral nervous disease associated with gonorrhoea cannot be maintained. Henderson and Richie state that the gonococcus may cause one of the rarest forms of cerebro-spinal meningitis. Fürbringer's patient was a young man with acute gonorrhoea and symptoms of cerebro-spinal meningitis: lumbar puncture was done *intra vitam* and *post mortem*, and the meningococcus was found.

Wooten describes the case of a man of 36 years of age, previously healthy, with a typical gonorrhoeal anterior urethritis, treated by injections, and followed by gonocystitis: after which he took medical advice. He had rigors, headache, backache, suprapubic and perineal pain. He was improving after a week, but three days later had a rigor, with a temperature of 103° F., bounding pulse, and psychic symptoms; also headache, nausea, vomiting, vertigo, and haematuria: the face was congested, pupils dilated and sluggish; reflexes exaggerated; the psychic symptoms developed into acute mania requiring restraint for three days, with temperature from 101° to 99·5° F.. There were hyperaesthesia, rigidity, and tremor of the neck muscles: arthritis followed; next trismus, retraction, deafness, upturned eyes, stupor developing into coma, with fatal result. The total duration of the meningitis was about three weeks. We cannot ignore the importance of such evidence as this.

Delamare quotes this case: he rejects Tixier's case of gonorrhoeal arthritis with purpura, violent headache and delirium, general congestion of the cerebral pia mater, and early pachymeningitis on the convexity of both hemispheres, as proved *post mortem*; also Jullien and Sibut's case, as showing no gonococci in the blood or vagina, no fever or roseolar spots, or symptom of meningitis. He accepts Stiénon's, whose patient, after four weeks of acute gonorrhoea, was seized with vomiting, rachialgia, headache, stiffness of neck, urinary incontinence, inequality of pupils, delirium, without any joint troubles. This man recovered in two months. He also accepts Reimer's similar case without arthropathy; and apparently Fürbringer's fatal case, in spite of the bacterial findings: also Boinet's girl with delirium, paraplegia, sacral sore, and coxo-femoral arthritis, with death in three months; though the *B. pyocyaneus* was found, and not the gonococcus; also the case of Guntz of a young soldier with gonorrhoeal arthritis rapidly followed

by cerebral meningitis ; and Danlos's, of an alcoholic patient 30 years of age, with syphilitic father ; the patient having acute retention of urine on the twelfth day of gonorrhoea, rupture of the urethra, occipital headache, tremor, wasting, multiple abscesses ; then an interval of a week, followed by coma and death in the third month. *Post mortem* there was ependymitis of the left lateral ventricle. No gonococci were found, but some diplococci and also *Staphylococcus aureus*. This is, at worst, a metastatic secondary infection indirectly due to a primary gonorrhoea.

Henderson and Richie have followed up their case with unprecedented vigour and persistence. A strong adult man with gonorrhoea suddenly developed headache and vomiting. Lumbar puncture gave cerebro-spinal fluid under increased pressure, with very numerous polymorphs and diplococci, which could not be cultivated either from this source or from the blood, but which were proved, according to the reviewers, to be gonococci. Gonococci were also found in the urethral discharge. It was held to be confirmatory that three mice which were inoculated intraperitoneally with cerebro-spinal fluid withdrawn on the tenth day were all alive eighteen days later ; which was not likely to be the case if the fluid had contained meningococci.

Henderson and Richie mention previous cases : Wynn's three patients with gonorrhoeal systemic infection ; in the second the cerebral meninges were cloudy and the subarachnoid fluid turbid and in excess, suggesting an early meningitis. A feeble growth of gonococci was obtained. In Prochaska's case the pus in the left cerebral ventricle and in the meninges contained Gram-negative diplococci and supposed gonococci were obtained in pure culture from the blood and *post mortem* from the meningeal pus, but they were not essentially differentiated from meningococci. Belke's, in which meningococci were found in the cerebro-spinal fluid and pus from the joints and seminal vesicle. Pick's, in which the isolated micro-organism again proved to be the meningococcus. And Rombach's case of a youth 19 years of age with acute cerebro-spinal meningitis. Polymorphs were found in the cerebro-spinal fluid and also intracellular and extra-cellular diplococci from which pure cultures of gonococci were obtained. No fermentation tests were performed : the diplococci would not grow on plain broth or agar. Henderson and Richie consider that the micro-organism was the gonococcus. Their verdict in Rombach's case, itself confirmatory of other equally strong evidence, carries conviction.

Luys's mention of Bieck's case has already been referred to under Psychopathy. His patient was a man 48 years of age, with a year's gonorrhoeal discharge, who developed a fresh infection, and *post mortem* a patchy exudate was found on the cerebral pia mater, especially right frontal and parietal, containing gonococci. Blind and Ricord remark that previous cases of gonorrhoeal meningitis have usually occurred comparatively late in the disease, and were chiefly spinal. Their patient was a strong soldier 30 years of age, who, after exposing himself on September 25, 1916, and again three days later, on the following day had a violent headache and rigor, and was admitted to hospital as ' meningitis, probably cerebro-

spinal': he had a marked Kernig with spinal rigidity, increased knee-jerk, Babinski, tendency to stupor, vomiting, temperature from 39·8° to 38·5° C.; no urethral discharge, but some moisture at the meatus; tache cérébrale. Next day a lumbar puncture was done, and the fluid was clear with normal pressure, and free from albumin, but contained a few leucocytes; but no micro-organism from smear or culture. Later there was urethral discharge containing very definite gonococci. After November 1 the patient improved rapidly. The writers' comment is that, after the patient's exposure to infection, the infective agent settled on the meninges, where the conditions were unfavourable, owing to absence of albuminoid substances and want of affinity of the endothelium. The rapid amelioration afterwards was due to the fixation of the agent in the urethra. The absence of gonococci in the cerebro-spinal fluid was held to be usual in such cases: the condition of the fluid would have warranted a denial of meningitis altogether if it had not been for the clinical symptoms. They reject the possibility of tubercular meningitis and the X-rays had shown clear lungs without any trace of tracheo-bronchial adenopathy.

On the whole, Henderson and Richie's case still probably affords the strongest evidence of a gonorrhoeal cerebro-spinal meningitis that has yet been produced; but the cumulative evidence of the literature is overwhelming: Wooten's, Stiénon's, Guntz's, Danlos's, Henderson and Richie's, Rombach's, Bieck's, Blind and Ricord's.

Meningomyelitis.

Stanley has described paraplegia in gonorrhoea, associated with kidney or bladder trouble, and held that the disease of the urinary organs produced a morbid impression on the cord by way of 'sentient nerves'. Gull considered that paraplegia in these cases was due to inflammation of the cord, produced in an analogous manner to the arthritis. He suggested that urethritis probably induced paraplegia either by a purulent or specific blood infection.

Raymond quotes Hayem and Parmentier as drawing attention to the frequency of the association of gonorrhoeal arthritis with spinal phenomena, and expressing the opinion that the nerve-roots undergo an inflammatory reaction, and that there must be a meningomyelitis; and quoting two cases of Bonnet, who attributes the nervous symptoms to gonorrhoeal arthritis. Charcot concludes that they are only indirectly due to gonorrhoea; that the spinal affection is arthritic in origin, and the existence of arthritis is an essential preliminary; while admitting that if a case could be found of gonorrhoeal spinal trouble without a joint affection, as has since happened repeatedly, it would be decisive against this theory.

Von Leyden had shown that many cases described as urinary paraplegia or reflex paralysis were really gonococcal myelitis. Moltschanoff had demonstrated changes in the nervous system due to the gonococcus, in the cells of the anterior

roots of the cord, with degeneration of the posterior roots and pyramidal tracts, and hydraemia of grey and white matter, and degenerative neuritis, and in one case disseminated sclerosis of the posterior and lateral columns. Kienboch states that polyneuritis, polyarthritis, myelomeningitis, and mononeuritis may be classed together as metastatic.

Delamare rebuts Charcot's suggestion, supported by Vulpian and Bouvier, of a primary arthritis acting upon the cord, which in return causes atrophy of muscles, on the ground that it does not explain cases where a monoarthritis leads to generalized atrophy, and implies a pre-existing arthropathy in all cases of spasmodic paraplegia, which we know does not exist. Finally, he concludes that we are driven to ask whether either gonococcus or gonotoxin is responsible. He mentions, as spinal changes, acute or chronic meningomyelitis reported by Home, Stanley, and Gull; the slighter types, suggesting functional change, being more frequent. In chronic cases of meningomyelitis there is little or no meningitis, and they are chronic from the first. After reporting some cases, he remarks that arthritis plays no rôle in their genesis, and that Bouvier refuses to accept them on that account, because he attributes gonorrhoeal spinal trouble to arthro-synovitis. Pissavy and Stévenon alluded to Prochaska, and remarked that he 'gave more definite proof'; having found in the purulent exudate of the cord and in the pus from the seminal vesicles 'micro-organisms having all the characteristics of the gonococcus'. Nevertheless, they add that secondary infections may play the principal rôle in some cases of meningitis. The gonococcal type has no differentiating characteristics: weakness, headache, rachialgia, stiffness of neck, vomiting, constipation, fever. They suggest that a good dividing line between the slight and severe forms is struck by the presence or absence of sphincter troubles, usually retention of urine followed by overflow, never present in benign nor absent in grave cases. They mention seven fatal cases out of a series of twelve from septicaemia, the focus usually being a sacral sore or bladder infection; also a case of Dufour, in which death occurred from bulbar complications, ascending myelitis, and disseminated lesions throughout the spinal axis. The course is usually rapid—about a month, but may be two and a half months.

The rare post-mortem examinations show softening of the cord, the meninges participating. In four cases known to them when bacterial examination was made, the importance of secondary infection was confirmed, *Staphylococcus albus* being found once, once no micro-organism, and a micro-organism, not gonococcus, in the other two cases. Their general conclusions are, that, having once admitted the rôle of gonorrhoea, there are only two alternatives, one being to subordinate all the phenomena to the joint lesions, the pains being due to the 'rheumatism', vertebral and other, the atrophy dependent reflexly on the pains; in reflex amyotrophies the tendon reflexes are always greatly exaggerated: the paresis is then attributed to the weakness and pain. But the other alternative must be accepted in some cases where there are pains, paresis, amyotrophy, and exaggerated reflexes, without joint manifestations; and this alternative is to attribute the

symptoms to slight meningomyelitis. It has also been confirmed by lumbar puncture, apparently in a case of their own, where bacterial proof was absent, but considerable albumin and very marked lymphocytosis were present in the cerebro-spinal fluid.

Batut includes among the spinal complications of gonorrhoea meningo-myelitis, chronic myelitis, functional myelitis; which, he says, are extremely rare, adding that he has failed to meet with a case in thirty years.

Allbutt and Rolleston, writing on myelitis, refer to thirty cases of Parry, Weichselbaum, Block, Wynn, and Prochaska.

Gordon states that it is now well established that the gonococcus can produce meningitis; in a case of his own the precipitin reaction of Vincent, absence of agglutination by antimeningococcal serum, and the failure of the latter to improve the patient 'decided the diagnosis'. The case was severe gonorrhoea, in the course of which the patient developed meningeal symptoms; repeated lumbar puncture was done, and a slightly cloudy fluid with abundant polymorphs was obtained, containing diplococci, with the opposed surfaces flattened. In spite of serum the patient died.

Chavrier and Février's Case. A healthy soldier, 22 years of age, without nervous or rheumatic heredity, or syphilis, alcoholism, or metallic poisoning, or trauma, had acute gonorrhoeal urethritis, rapidly declining to a gleet. The following fortnight he had headache, rigors, and anorexia, accompanied by ankle cramps and choreic movements of the right shoulder with flexion of the head to the same side; tremors, and hiccough-like respiration; convulsions of legs; fibrillary twitchings of upper lip, lumbo-sacral pain, and sciatica; spinal tenderness; exaggerated knee-jerks; joint pains and tenderness, with swelling; slight fever; crepitus; atrophy of thigh; no hemianaesthesia or restriction of visual field; great improvement after a few weeks. The writers seem to admit the possibility of hysterical chorea; but exclude it owing to the absence of hemianaesthesia, &c. The diagnosis suggested is a spinal meningitis of gonorrhoea involving the whole length of the cord; but it is somewhat curious that they consider the success of salicylate treatment as confirmatory evidence of the gonococcal origin.

The clinical picture is somewhat too hazy for any definite diagnosis, and suggests a functional rather than an organic condition.

Spillmann and Haushalter report two cases. *Case I.* A woman of 26 years of age, pregnant $7\frac{1}{2}$ months, when she noticed a discharge. She had a normal labour followed by atrocious pain in the legs, knees, and foot. She was pale, anaemic, spare, cadaverous looking; suffering from insomnia and nervous excitement, with deep sacral sores, the size of the hand; the left knee full of fluid, pain preventing the movement of the limbs; whitish yellow vaginal discharge; difficult to detect gonococcus owing to the number of micro-organisms; pain slightly less a month later; swelling of knee persisted; five weeks later, lancinating pains and white oedema in both legs, especially right; reflexes apparently preserved; slight tremors of the legs on movement; could with difficulty lift legs

to level of bed; later had a convulsive crisis. It should be mentioned that the reflexes could not be properly explored owing to pain. On January 1 oedema was diminishing; no fluid in the left knee: great atrophy of the legs. Ten days later, sores much improved and atrophy less; tenderness over great trochanter and slight shortening of the left leg; could walk a little with help. Pain was lost during the next year; but there was ankylosis of the left knee and hip; reflexes and sensation normal: slight atrophy remained; could walk with short steps, slightly dragging feet.

Case II. Woman, 29 years of age, typhoid at 11 years, had a miscarriage a year previously. About seven months later noticed that her husband had an urethral discharge, and a few weeks afterwards herself had a yellow vaginal discharge, followed in a week by pain in wrists and, two days later, pains in the left knee; lancinating pains in both legs and could not move in bed; anorexia, photophobia, and meteorism; some fluid in both knees; but the swelling chiefly due to thickening of periarticular tissues; joints excessively tender, hip and foot free, but right foot atrophied, calves and thighs atrophied; skin of legs dry and wrinkled, knee-jerks could not be explored; small sacral sore which increased, during December, to the size of the palm of the hand. Temperature 38·5° to 37° C.; rigor in middle of January; erysipelas. A month later, appetite returned and the patient improved; but discharge persisted. There was atrophy of muscles, especially of the thigh and knee and ankle, with nervous agitation. At the end of April could take short steps with difficulty; early in May, pains in left knee, but there was almost complete ankylosis: passive movements, limited, painful, and crepitant, but reflexes were normal, and the patient could now raise her legs easily. After a visit to Plombières the pain had almost left the muscles, and the patient was much improved.

The similarity of the two cases was naturally commented upon by the writers, and it is concluded that the nervous system was organically involved, either peripherally or in the cord, and that the symptoms ought to be referred to diffuse meningomyelitis. Both of these cases, if standing alone, would only furnish very doubtful evidence of either gonorrhoeal neuritis or meningomyelitis; but the second, at least, suggests very strongly a connexion between gonorrhoea and the supervening nervous symptoms, whether the arthropathy was an intervening episode or vice versa.

Osler, writing on myelitis, remarks that sometimes multiple arthritis is present. Charcot's theory that gonorrhoeal spinal affections could not occur without intermediary arthritis has been disproved by subsequent cases.

Raynaud mentions Moreau's case, a youth of 20 years of age, with great pain and swelling of the left knee; general muscular atrophy, great weakness, green diarrhoea, urine scanty, white oedema of the left leg, sacral sore, death in a week. Raynaud offers a diagnosis of rapid myelitis and remarks that it is a pity a bacteriological examination was not made. Unless some features of the history have escaped report, however, the clinical evidence is fairly strong. One does not wish to undervalue the extreme importance of bacteriological

confirmation; but it is equally important not to overvalue it. The weight attached to such evidence seems to depend in a large measure upon the type of mind of the investigator, the mathematical, scientific mind being impatient of any proof except such as can be set before the senses. Other evidence arrived at by a process of reasoning and inference from clinical appearances is to such a mind essentially lacking; but, like circumstantial evidence in a criminal case, it may be stronger than direct evidence: which owing to some unknown factor or some error of technique, might be misleading.

Raynaud also describes Gémy's case of a man of 24 years of age, free from syphilis or alcoholism, who entered hospital on November 29, 1887. Three years previously had a slight gonorrhoea, and ever since a pain in the left tibio-tarsal joint and right knee, foot, and right arm, also in the lower jaw, so that for a month the patient could not open his mouth. There was no urethral discharge at the time and, with difficulty, the patient was able to rise. In March there was sacral pain and slight temperature. The joint trouble shifted like ordinary rheumatism; there was paraplegia but sensation was preserved; sudden pains in the knees and legs; the patient felt as though 'his flesh were being torn'; reflexes diminished; seemed to be 'walking on needles'. In June there was a further attack of 'rheumatism', and knee-jerks were almost abolished; lumbar tenderness, tingling, and tremors in the legs and numbness, pains radiating from the spine; in the middle of October the spinal trouble disappeared; but there was still slight 'rheumatism' again, with crepitus in the affected joints, and passive movement in the right tibio-tarsal joint produced excessive pain. The ankle remained painful and inflamed at the end of February, but general condition had much improved. Raynaud admits the doubtful character of the case owing to the absence of sensory symptoms and sphincter troubles and the presence of arthritis, but says he has no doubt from long study of other cases that gonorrhoea may be charged with spinal symptoms.

Speranski reports the case of a man, 25 years of age, with a stricture in April, 1892, from a chronic gonorrhoea and with pain and swelling in the elbow; for seven years he had been alcoholic and had neuropathic heredity. Two years previously, had delirium tremens, followed by gonorrhoea. A few gonococci were found in the chronic discharge. By the end of July the pain and swelling of the elbow had improved, but reappeared in the right shoulder. In September he began to have weakness in the legs and sometimes cramp-like tremors. Knee-jerks were exaggerated, especially the right; movements of the right shoulder and elbow painful and difficult; muscles of right arm atrophied, with diminished sensibility to touch, pain, and temperature; tenderness of lower thoracic vertebrae. In October there were anaesthesia and paraesthesia of both legs, sciatic pain, numbness in the thorax and diminished sensibility about rectum and scrotum, pains in the joints of arms and legs; and increased weakness in the legs and girdle pains. While in this condition patient was lost sight of. The comment is to the effect that many of the symptoms might be polyneuritic, while a few suggest involvement of the spinal membranes, whether

attributable to gonococcus or gonotoxin or associated staphylococci or streptococci, 'requires further observation'. This case will be referred to under Other Neurites, &c. It is difficult to determine the possible importance of the alcoholic factor.

Wooten's case of a man of 36 years of age of good previous history, no tuberculosis, syphilis, nephritis, or trauma; acute gonorrhoea, for which he treated himself with local injections. Then he got gonocystitis and took medical advice. He appeared with coated tongue, fever, and constipation, had two rigors the previous night: had backache, headache, suprapubic pain and pain in the thigh and perineum, with profuse purulent urethral discharge. Another chill followed; but in six days he was able to sit up. Three days later he had a rigor with temperature 103° F. and bounding pulse; was hilarious but fairly rational; headache and vertigo, nausea and vomiting; urine high coloured, scanty, muco-purulent and bloody; micturition painful. For three days he had acute mania, requiring restraint; temperature 99° to 101°, pulse 78 to 84; pupils somewhat dilated and sluggish; reflexes exaggerated; tremor; hyperaesthesia of skin, commencing tremors and rigidity of the neck muscles, with great pain and emotional disturbances; not alive to his surroundings. Towards the end of his excitement gonorrheal arthritis developed in the left elbow and right knee; trismus and retraction; the eyes rolled inwards and upwards; considerable deafness; hiccough; muttering delirium; ten days' stupor; coma; death. This case was described in the *Lancet*, 1889, as acute gonorrhoeal meningitis; which appears to be a very straightforward interpretation.

Eulenburg describes as gonorrhoeal myelitis the case of a man, 40 years of age, with gonorrhoeal endocarditis and polyarthritis. The first infection with gonorrhoea was ten or twelve years previously; re-infection two years previously; afterwards arthritis of elbow and knees and vertebrae, the third and fourth dorsal, and ankles, with temperature 39° C. The joint troubles recurred the following year, and at the same time there was anterior urethritis, with very numerous gonococci; mitral systolic murmur; absent knee-jerks, which afterwards returned to a slight extent; severe pain in the back up to the cervical vertebrae, with increasing inability to walk and difficulty in all movements of the legs and trunk; marked girdle pains in the lower ribs. Atrophy of the right thigh, especially extensors, also in calves; lancinating pains in the legs; weakness of reflexes of bladder and rectum; complete recovery three years after the first involvement. Bodily movements and mental condition appeared normal. The clinical picture here again is convincing.

Delamare quotes Chavrier and Février's case of the young soldier described above. He divides cases of meningomyelitis into acute, subacute, and chronic. Acute were cases of Stanley, Gull, Tixier, Pombrach, and five others. The symptoms, accompanying gonorrhoea, are sudden faintness, rachialgia, dorsal or lumbar pain, and paralysis of legs quickly reaching its acme; less commonly an ascending myelitis, cervical paraplegia reaching the bulb, generally but not

always spastic, always accompanied by sphincter trouble, sacral sores in all fatal cases; fatal eight times out of eleven; sometimes generalized amyotrophy. He gives a list of post-mortem findings, which he describes as very rare: Stanley, congestion of cord and meninges; Gull, softening of dorsal lumbar cord; Dufour, softening of cord from cervical to lumbar with granulo-waxy degeneration, false arachnoid membrane congestion, and interstitial sclerosis of the lateral pyramidal bundles; Barié, meningeal inflammation and softening of the lumbar cord. Only four cases were complicated with arthritis.

Subacute were Hayem and Parmentier's first case; two of Spillmann and Haushalter, in the first of which, however, gonococci were found in the vaginal secretions; cases of Polozoff and Duval: four out of five recovered, one of the former having a sacral sore.

Chronic, probably functional, were Reynault's, in which there was absolute paralysis of legs and lumbar pain, which became less, and the patient could take some steps; spasmodic paraplegia with retention and then incontinence of urine supervening gradually without any sore or objective sensory trouble or great amyotrophy; sudden disappearance of the symptoms with reappearance three years later. Millet and Bouvier's, no increased reflexes; 'spinal trepidation', some pains in the legs without true paralysis or sphincter trouble; rapid recovery. Intermediate forms exist, which, according to the writer, cannot be grouped. Bouvier quotes three cases of Millet and three of his own, apparently functional myelopathies; strong reflexes; inconstant muscular atrophy; usually pains in the limbs; and states that the trouble invariably coincides with arthrosynovial manifestations.

Charcot's case was a Hungarian, 26 years of age; had numerous gonorrhoeas with arthritis, spasmodic atrophic paraplegia of the legs, and convulsions; no sensory or sphincter trouble. Then we have Hayem and Parmentier's case of a coachman, described under Kienboch; Rendu's man, 32 years of age with arthritis of the right knee, lumbar pain and paraplegia, incomplete without sensory trouble, followed by general muscular atrophy; Williams's case of spasmodic atrophic paraplegia, with arthralgia and deformity of feet; Launet's polyarthritis deformans with increased reflexes, followed by general muscular atrophy, sacral sore, and keratodermia.

Delamare has four cases of his own. Three had bilateral spinal symptoms, with unilateral joint trouble; one had no joint trouble; a typical example, that of a man, 33 years of age, denying any alcoholism, and without any stigmata of any, had influenza at 22 years of age, rheumatism at 27 years of age, cured by salicylates without cardiac sequelae; no nervous defects or appreciable hereditary predisposition. On August 6, 1900, the patient had a very slight first gonorrhoea, with thigh pains four days later, left sciatica, followed next day by right; right knee and ankle swollen and painful, and then arthritis of the right wrist; fluid in the right knee. A month later joint troubles had disappeared, but there was still lumbar pain reaching down the legs, with slight atrophy of right thigh and very strong reflexes; 'epileptic trepidation'; plantar and cremasteric reflexes

absent; little sphincter trouble; both legs cold and 'violaceous'; muscular power intact; only pain prevented walking; complete recovery in a fortnight. There is perhaps little here that might not be attributed to the reflex effects of so-called gonorrhoeal 'rheumatism'.

Kienboch mentions Peter's cabinet-maker, 28 years of age, with a third attack of gonorrhoea, the first two attacks being without complications; bilateral sciatica two and a half months later, tenderness of lumbar and sacral vertebrae; girdle pains, motor weakness, and sensory disturbances in the legs, no sphincter trouble or fever; later, transitory pain in the left jaw; pain and swelling in the right knee a month after the beginning of the nervous symptoms; two weeks later, paraesthesia in the soles of the feet. The same criticism applies as in the last case. Von Leyden diagnosed this as an affection of the spinal cord. Fournier, in a discussion on the paper, expressed the opinion that we were dealing with a disease of the sciatic nerve, as a consequence of a purulent arthritis. Kienboch also mentions the first case of Hayem and Parmentier, a man, 26 years of age, without hereditary rheumatism, nervous disease, or syphilis; typhoid at 16 years of age, slight alcoholic tendency; gonorrhoea May, 1883, after three weeks becoming a gleet; then vague pains in the right shoulder and hip and left ankle, and stopped work; urethral discharge returned; hospital in September and left in December, though he still had pains in the feet and at the level of the right knee; four months later pains spread upwards to the chest. Re-entered hospital in 1884, soles painful, girdle pains, pricking and tingling in the feet, legs, and calves, with very rare lightning pains; in October the pains were worse and lancinating, and the dorso-lumbar spine was tender and the knee-jerks much exaggerated, especially right; epileptiform tremor and loss of muscular power; the muscles responded to faradism; in March fresh pains in the right shoulder; in April recurrence of dorso-lumbar pain; no pain except in the ankles at the end of May, but joints restricted and crepitant; the patient dragged his feet; reflexes very exaggerated; sensation normal. When he left hospital, discharge had been absent three months and joint condition much improved, atrophy less marked, reflexes normal, no tremor; bilateral crepitus of the shoulder and knees; still dragged feet slightly, walked fairly, and able to resume work; spinal column had lost some suppleness. Hayem and Parmentier considered that a single cause was suggested for the rheumatism and spinal phenomena, which seems probable. It would, however, be difficult to insist upon any definite spinal lesion.

Pissavy and Stévenon report on a youth who at 19 years of age had a first gonorrhoea, complicated by joint trouble, for six months. He did not come under notice until he was 30 years of age. A year before this the joint trouble had returned and with it cystitis, though without any urethral discharge, and pains in the knees and ankles. He entered hospital with an abundant discharge, diffuse vertebral pain with much tenderness; pains spread to the legs; girdle constriction and some lancinating pains in the arms, no headache or sensory trouble; tenderness at the insertion of tendo Achillis and about the knees, elbows, and wrists, but no swelling and passive movements fair; deep reflexes exaggerated;

'epileptiform tremor' only when the patient held himself stiffly. Muscular atrophy in all limbs, especially legs, and most in right thigh, tendency to Kernig, slight electrical hyper-excitability in the limbs; no reaction of degeneration, sphincter trouble, sacral sore, or fever, or history of syphilis; he did not improve, but had no further complication at least for two months.

Henderson and Richie refer to Hayem and Parmentier's six cases, the first of which has been described under Kienboch. The second is complicated by syphilis.

Case III. The patient entered hospital on November 3, 1865, with weakness of legs and double sciatica, worse on the left side; could not stand long; no fever or sphincter trouble; had been exposed by working in a hangar; gonorrhoea was discovered; third recurrence and still muco-purulent after three months; after a fortnight the pains were nearly gone, but weakness and numbness persisted, the discharge being much less; then, pain in the temporo-maxillary joint; pains in the leg returned, and after a week, in the right knee; practically cured by December 6. The case is quoted as an instance of the principle that double sciatica in gonorrhoea is symptomatic of cord involvement; but this latter complication is hardly established by the symptoms.

Case IV. Healthy youth 19 years of age with previous rheumatism; had an attack of gonorrhoea, followed in three weeks by pains in the shoulders, arms, and vertebral column; movement difficult; almost complete paraplegia reaching nearly to the attachments of the diaphragm; analgesia and anaesthesia of legs, and restlessness; urination by overflow; bladder nearly to the umbilicus; reflexes very pronounced; persistence of discharge; some ulcers in the region of the frenum, shallow and not indurated; while in hospital had an attack of choleraic diarrhoea. The spinal involvement can hardly be doubted, and we must attribute this either to an incredible failure to recognize syphilis, or to ulcus molle, or to gonorrhoea: and can hardly hesitate about the choice.

Case V. Man of 28 years of age; gonorrhoea June 17, 1855; next month pains in the shoulders, and next day in the legs; then dragging of the legs; two days later could not rise or urinate; then incontinence of urine; when he reached hospital could hardly move legs; girdle pains in chest; urethral discharge; considerable improvement in ten days, and soon left hospital; next year got a new infection and similar symptoms. This is another strong case.

Case VI. A man with gonorrhoea in 1797; several previous attacks treated by injections; discharge disappeared, but was followed by sciatica and spasms and violent pains in the loins and knees, coincidently with chronic urethral discharge; in 1799 another gonorrhoea and another sciatica, the pains reaching to the intercostal muscles; in bed four months, and life in danger; pain in the legs with great weakness; was found to have a stricture, cured by cautery; the nervous symptoms then disappeared. The apparent absence of sphincter involvement in such a grave case seems exceptional; but spinal involvement would appear to be fairly established.

Henderson and Richie mention three cases of Wynn. In the second the

cerebral meninges were cloudy and the subarachnoid fluid turbid and in excess, suggesting an early meningitis; no gonococci were found in the films from the cardiac valves, lungs, spleen, kidneys, or meninges; a feeble growth of gonococci was obtained on blood agar from pus in the vesiculae seminales and the pelvic abscesses, but not from that in other situations; there were also colonies of staphylococcus and *B. coli*. In the third case the subarachnoid fluid was in excess and turbid, and there was no pus in the meninges or brain substance; the heart's blood *post mortem* yielded typical gonococcal colonies in pure culture. None of these can be excluded.

In Prochaska's case, the micro-organism said to be the gonococcus were obtained from the blood during life and from the meningeal pus *post mortem*; and pus in the left seminal vesicle and meninges containing intracellular diplococci; but the possibility of meningococci cannot be definitely excluded.

In Rombach's case the patient was a youth 19 years of age with acute cerebro-spinal meningitis. De Jong conducted a bacterial examination of the cerebro-spinal fluid and a pure culture of gonococci, expressly stated not to be meningococci, was obtained; the microbes were both intracellular and extra-cellular, and would not grow on ordinary agar or broth. No fermentation tests were performed.

Gower's case was a man 22 years of age, admitted to hospital on August 24, 1910: he had gonorrhoea two months previously, the discharge lasting a fortnight, and the patient remaining at work. On admission there was no discharge: on August 27 there was slight frontal headache and neuro-retinitis followed, and there was evidence of old iritis in one eye; early in October there was pain in the left knee, and afterwards in the foot, spreading to the groin: then pain and weakness in both legs, numbness of left hand, retention of urine necessitating catheter; and weakness spreading to the trunk, so that the patient could not sit up; loss of sensibility in the legs and loss of sensation in trunk; if the catheter were not used daily the temperature rose. After the first week the electrical reactions to galvanism and faradism were weakened in both legs. When the report was made the patient was still in hospital. It was suggested that this patient had a collection of gonococci on the spinal cord, as well as on the optic chiasma. This is only inference; but no other cause than gonorrhoea seems to have been elicited.

Luys's case was that of a youth with gonorrhoeal vesiculitis, who had been treated with irrigations, and had sudden acute retention of urine; the left seminal vesicle was slightly affected, having a few nodules without being swollen; nothing was found in the prostate or Cowper's glands; there were signs of spinal irritation with considerable dilation of pupils; the knee-jerks were excessive, and there was ankle clonus. Whatever may have been the path of infection, the spinal symptoms may again fairly be attributed to the gonorrhoea. The patient was cured by rest in bed combined with catheterization.

Such is the evidence in favour of a gonorrhoeal meningomyelitis; and one who would deny the existence of such a nervous complication on gonorrhoea sets out on a path crowded with formidable obstacles.

Peripheral Neuritis.

Spillmann and Haushalter are inclined to disagree with those who place gonorrhoea among the genito-urinary affections capable of determining troubles of the spinal cord. They suggest that the cause which in gonorrhoeal spinal complications acts upon the cord is yet unknown; that the symptoms in certain cases might also be attributed to polyneuritis localized to the legs, afterwards mounting to the root zone.

Kucharzewski's patient was a butcher, 22 years of age, with gonorrhoeal arthritis, fever, both knees and wrists swollen and tender, thick pus in the anterior urethra, posterior urethra clear, gonococci found in the pus: iritis supervened: the knee-jerks were much exaggerated: there were girdle pains and substernal pain, paraesthesia, hyperaesthesia, and paresis of legs: almost complete recovery in six weeks, except for the eyes. The paraesthesia consisted of tingling and vague pains in the legs. There was no previous history of syphilis, rheumatism, or nervous or ocular trouble. The muscular power in the legs was affected, but the movements were free. Kucharzewski attributed some of the symptoms to a slight or abortive polyneuritis, but did not suggest that such a diagnosis could be definitely made.

Kienboch relates the case of a pregnant woman, 26 years of age, always healthy before marriage, which took place in August, 1899. She was infected by her husband with gonorrhoea and a year afterwards had fever, dragging pains in the legs, swelling and pain in both arms, followed by paralysis; was confined to bed for six weeks in February, 1900. No gonococci were found in the cervical discharge. The deep reflexes were exaggerated, except that the right triceps and biceps reflexes were absent. There was atrophy of the left arm and the left ulnar nerve was tender; electrical excitability was reduced in the left arm.

He describes Dercum's case, a man 36 years of age, who three weeks after gonorrhoea had a spreading arthritis followed by atrophy of the arms. Paresis in the legs prevented walking for three months, and the atrophy spread to the legs with fibrillary tremors in the affected muscles. Dercum's diagnosis was 'muscular atrophy associated with gonorrhoeal rheumatism', but Kienboch thinks it was multiple gonorrhoeal neuritis and arthritis. The patient improved.

Then Lévy's patient, a man 26 years of age, whose gonorrhoea was followed after several months by very severe pain in the left thigh, ankle, and leg, and tenderness in muscles and nerves. The patient improved and relapsed. The knee-jerks were very exaggerated; and there was swelling in the right fingers and right shoulder.

Also Lévy's second case, a man of 35, who had tuberculosis of the right knee-joint at 14 years of age, followed by atrophy; and gonorrhoea at 22, with very free recurrent discharge, the last attack being followed by shifting pains in the limbs and joints, tenderness of heel, atrophy of legs, exaggerated knee-

jerks, hyperaesthesia of skin, ankylosis of right knee. Electrical reactions were disturbed; but there was no reaction of degeneration.

Next Poubrak's, a man of 22 years of age, who after a week's gonorrhoea had retention of urine, pain in the left knee and ankle, followed by weakness and atrophy of both legs increasing to paraplegia, with absent knee-jerks, tenderness on deep pressure, lancinating pains, cachexia, sacral decubitus, and death in three months.

Naunyn's was a girl of 17 years of age with three months' gonorrhoea, followed after some months by inflammation of the left elbow and knee and neuralgia of the right leg; atrophy and limitation of movement, and pain on passive movements; tenderness of sciatic and crural nerves. Also a second case, a male with gonorrhoeal endocarditis and arthritis and crural neuralgia followed by paralytic weakness and muscular atrophy.

Bloch's, a man with gonorrhoea followed eight days later by pains and weakness in the legs; temperature and other signs of infection, inflammation of the right knee and hip; double crural and sciatic neuritis; tenderness of nerves and muscles, spasm, hyperaesthesia, tremor, atrophic paralysis, diminution of electrical excitability. Bloch inferred from the fact that the nervous disturbance was similar on both sides and the joint trouble not, that the neuropathy was not arthrogenous. The symptoms in the left leg flew to the right; swelling of the right knee only improved gradually, resulting in partial ankylosis of knee and hip with atrophy of thigh. Four months later the gonorrhoea and general condition were relieved.

Kienboch also mentions Treves's case, a man 22 years old with gonorrhoea, followed by stiffness of the body, weakness and cramp in the left arm, pain and tenderness in the calves; the upper arm became swollen and there was fever: recovery in three weeks. In this case he points out the difficulty of deciding whether there is neuritis as well as myositis.

Raymond and Cestan describe the case of a commercial traveller 44 years old, who, at 22 years of age, had an uncomplicated gonorrhoea for a month. There was no history of syphilis or plumbism, but there was an alcoholic 'burst' ending in October, 1900, and on November 20 a fresh infection with gonorrhoea, followed in a week by lumbar pain, weakness, wasting, pains in the legs, feebleness of gait; slight Romberg; had to watch his feet in walking; no steppage gait or ataxy or loss of sensation in the feet; weakness in the extensors of the thighs; Achillis reflex absent, also right knee-jerk, the left being obtainable on reinforcement, tenderness of calf and thigh muscles, slight atrophy inside calves and thighs; no arthritis; reacting pupils; slight want of electrical excitability in thigh adductors, especially left. This was diagnosed as pseudo-tabetic polyneuritis without reaction of degeneration, and of very favourable prognosis.

Ménétrier reported a 'gonorrhoeal polyneuritis followed by death from intercurrent broncho-pneumonia'. The patient was a man 46 years of age, who, a month after the onset of gonorrhoea in April, 1904, was seized with pain and

inability to move a limb, first legs, then arms. He had had several previous gonorrhoeas, the discharge always lasting several months; was admitted to hospital six months after onset with a copious purulent gonorrhoeal discharge, practically complete paralysis of legs, adductor atrophy, and to a less degree atrophy of calves and quadriceps, hyperaesthesia of muscles, tenderness of nerve trunks, lancinating pains and 'pins and needles', absent knee-jerks; paralysis of arms less, but the atrophy was marked, also muscular inco-ordination, difficulty in rising to a sitting posture, though the trunk muscles were not markedly atrophied; there was always reaction to faradism in the legs, but the reaction was altered in the arms: muscles of neck and trunk became involved; then a bedsore appeared; next fever, dyspnoea, râles at the right base, and death in the middle of November. *Post mortem*, the pia mater was congested and the white matter injected; there was no meningeal exudate; cerebro-spinal fluid normal; the spinal pia mater highly vascular but not the cord tissue: the large nerve trunks appeared intact and the only change in the muscles was atrophy; kidneys congested, soft, and swollen, mucous membrane of bladder congested; lungs dense at both bases; pus squeezed from bronchioles. Microscopically in the cord, chiefly cervical and lumbar regions, there were changes in the anterior cornual cells. The lesions of the peripheral nerves were most marked: e.g. in the radial there were no normal fibres, disintegrated myelin throughout, and the sheath here and there distended; axons swollen and fragmented and in many places had disappeared. In the large nerve trunks the changes, though present, were less marked; there were changes in the nerve roots, but these decreased as the centres were approached. Ménétrier considered this a good example of polyneuritis, the gonorrhoeal origin of which cannot be doubted, the effect being due to auto-intoxication.

A quest for a purely peripheral neuritis without spinal involvement would necessarily be disappointing. Why, indeed, should any toxaemia presenting the features of that nervous disorder confine its evil activities within the bounds of any particular entity which happens to be clinically convenient? Thus an alcoholic multiple neuritis may be complicated by the other destructive effects of alcoholism, for instance upon the central nervous system. In a gonorrhoeal multiple neuritis similarly we must expect a complex picture, and we may accept it if it include the symptoms ascribed by common consent to that disease.

The lapse of time between the gonorrhoea and neuritis in Kienboch's case and that of Naunyn's girl patient does not rule them out; but the symptoms of the latter are not very satisfactory, while the former may probably be accepted. In Dercum's case, Kienboch's diagnosis is possible, but Dercum's more convincing. Of Lévy's two cases neither is typical. Naunyn's male patient has suggestive symptoms as far as they go; while those of Poubrak go too far, yet cannot be rejected altogether. Bloch's is a fairly good case: Treves's only possible. Raymond and Cestan's two cases, though complicated, are on the whole rather to be accepted than discarded: and Ménétrier's affords strong evidence of a polyneuritis almost obscured by graver features. If we cannot

produce more conclusive and exclusive evidence, we find clinical phenomena as strongly suggestive as we can reasonably expect in an inquiry bristling with difficulties.

Other Neurites, Neuralgias, &c.

Coutagne refers to Fournier's memoir and the coincidence of sciatic neuralgia with gonorrhoea, inferring that certain sciaticas were manifestations of 'gonorrhoeal rheumatism'; and Coutagne asks whether we are to accept this as a pure coincidence or to conclude that a more or less prolonged irritation of the urethra can produce a painful explosion in the neighbouring nerves; or can neuralgias enter the category of gonorrhoeal rheumatism?

Raymond quotes Brisson to the effect that gonorrhoeal sciatica is characteristically of short course, rarely more than a fortnight; seldom occurs in the first week, but may appear suddenly three weeks after onset of the primary disease, and is sometimes accompanied by cramps in the thighs: is rarely bilateral: pain spreads outwards, sometimes in the thigh and sometimes to the abdomen, and in a downward direction reaches the popliteal space: and quotes Charcot to the effect that gonorrhoea in the male seems to determine sciatica in the same way that it determines pelvic disease in the female, and Mauriac for a reflex theory of lumbo-abdominal or sciatic or crural neuralgias from orchitis. He adds that some cases of sciatica may be part of meningomyelitis rather than neuralgia or neuritis. Hayem and Parmentier state that double sciatica is usually secondary, and in the course of a gonorrhoea is referable to the cord.

Glynn quotes Raymond as authority for the statement that all intoxications seem to be capable of developing neuritis in a subject of neurotic constitution, and adds that experiments have shown that gonotoxin can act on nerve tissue.

Eulenburg mentions eight cases of gonorrhoeal neuralgia in the region of the sacral plexus, one affecting the sensory nerves of the arm, especially radial and median; six involving the main sciatic trunk as true sciatic neuritis and perineuritis, but two of these were limited in range, one being a case of achillodynia: there were five cases of involvement of other nerve tracts in sciatica. Six cases were female, three being bilateral. In one case the ulnar nerve was affected coincidently with the sciatic, and in three cases branches of the lumbar plexus. In the male cases there was almost always bilateral epididymitis and sometimes prostatitis, and cystitis as well. The gonococcus was found in the urethra in most cases either at the time of or shortly after the neuralgia.

Kienboch forms a list of nerves that may be implicated in gonorrhoeal neuralgia, &c.: lumbo-sacral plexus, obturator, femoral, ilio-inguinal, ilio-hypogastric, sensory nerves of urethra and bladder, radial, ulnar, and median. He adds that slight neuritis and neuralgia are not uncommon in gonorrhoea, usually appearing quite suddenly in the second week, and soon disappearing. In the diagnosis of neuritis, motor paralysis and tenderness of the nerve trunk are in its favour, though tenderness and paresis belong also to myositis, and swelling is in favour of the latter.

Delamare summarizes the gonorrhoeal neuralgias as lumbo-abdominal, crural, tibial, median, radial, trifacial, and, by far the most common, sciatic; the last being usually a neuralgia, very rarely a neuritis; sometimes purely nervous, sometimes accompanying an involvement of the cord. He accepts Home's case (to be described) with reserve as amounting to nothing more than the fact that sciatica returned and recovered with the gonorrhoea. He mentions that in one series of cases of gonorrhoea Fournier described 15 per cent. as complicated by sciatica: in seeking for its basis he points out that it recovers with the discharge and vice versa, and usually occurs in the second week of infection, and, above all, during joint complications, with which it sometimes alternates: it is much more common in the male, and he only seems to have known at that date of one published female case. The basis of the sciatica is unknown, the theories being reflex, rheumatic, and toxic: the only proved predisposing cause seems to be cold, although others have been suggested, e.g. the rheumatic diathesis, the lymphatic temperament, fatigue, and even masturbation.

Lilian and Jones state that without arthritis we may have sciatica both in acute and chronic gonorrhoea, and that probably the nerve sheaths are attacked by a systemic infection in the same way as the synovial and periarticular tissues are attacked in arthritis; and quote Gowers to the effect that tenderness of the nerve trunk is proof of neuritis, and Oppenheim as suggesting that some cases are transitional between neuralgia and neuritis; while they incline to the opinion that neuritis should be restricted to cases of muscular atrophy, sensory changes, and trophic disorders, reserving neuralgia for the instance where degenerative changes are entirely absent.

Hayem and Parmentier quote Home's case of a man with a fresh gonorrhoea in 1797 after many previous attacks. The discharge disappeared after injections; but was followed by sciatica and spasms, and pains in the loins and knees: two years later both gonorrhoea and sciatica recurred, and the neuritis extended to the intercostal muscles, placing the patient's life in danger. The symptoms disappeared after a stricture had been discovered and cured. They had another case, that of a man who entered hospital on November 3, 1865, with double sciatica and weakness in the legs, worse on the left side: there was impairment of sensibility with girdle pains, limping gait: patient had worked under exposure in a hangar: he still had a muco-purulent urethritis from the third recurrence of a gonorrhoea, after three months. In a fortnight the pains had nearly ceased and the discharge decreased; but weakness and numbness persisted: then he got pains in the jaw, and the leg pains returned, and in a week the right knee was involved; but he was practically cured after a further period of three weeks. It will be noticed that in this patient the joint involvement apparently succeeded the sciatica.

Coutagne relates two cases. *Case I.* A youth of 18 years of age, without family history of rheumatism: had worked in damp surroundings (for which compare the last-mentioned case) for two years without suffering: there was no venereal disease previously, but he became infected with gonorrhoea, followed in

less than a fortnight by pains in the knees and next day in the elbows and shoulders, but no swelling. Was practically cured in about two months, but promptly incurred a second infection, returning to hospital six days after discharge, with left crural and scrotal neuralgia. The patient improved and was discharged on his own demand about twelve days after re-entering the hospital. The pains did not pass the knee-joint.

Case II. A strong youth, 20 years of age, without personal or family history of rheumatism, had gonorrhoea with several recurrences during two years, having been badly attended to. The original attack was followed in about three months by deep pain outside the right thigh, which disappeared three and a half months before he appeared for treatment. When examined a new pain had appeared in the line of the right crural nerve. There was swelling of the glands with purulent discharge and right crural neuralgia, which did not pass the knee. Then pains appeared in the knees and elbows with considerable restriction of movement, while the neuralgia had almost disappeared: nearly a month later there was sciatic pain. The urethral discharge persisted, though less copious. Then the crural neuralgia reappeared, the sciatica disappearing. The patient was improving when he was discharged for disciplinary reasons.

The case of Chavrier and Février, diagnosed as a gonorrhoeal infection involving the whole length of the spinal cord, disclosed among its symptoms lumbo-sacral pain and sciatica. Raymond mentions two hospital cases at Lyon, published 1870, of crural neuralgia from gonorrhoea. Naunyn reports on a youth of 17 years of age with gonorrhoeal arthritis in the left elbow and knee, a few weeks after the onset of gonorrhoea, and, almost simultaneously, neuritis in the right leg with hyperaesthesia. In Allard's case, quoted by Ward, of multiple neuritis, we find among the symptoms crural and sciatic neuralgia. In Speranski's case, described under Meningomyelitis, there was sciatica six months after onset of the disease.

Eulenburg mentions a man, 22 years old, suffering from three months' neglected gonorrhoea, afterwards treated for two months and apparently cured; but severe pain followed, involving ilio-inguinal, left obturator, and then left sciatic, and afterwards right. He was cured of the neuralgia in a month. Peter's cabinet-maker, mentioned by Kienboch, has already been referred to as suffering from vertebral neuralgia; a case diagnosed by Fournier as sciatica.

'Lancinating pains' are a symptom frequently mentioned, e. g. by Kienboch, Eulenburg, and Naunyn, and need not be more than noticed. Kienboch mentions a woman of 26 with gonorrhoeal bursitis, arthritis, &c., including the symptom of neuritis of the left ulnar. Bernhardt gives an interesting description of a man of 26 with a first gonorrhoea complicated with orchitis: reinfected May, 1905, developing an inguinal bubo, and admitted to hospital in July: pain in the right arm from axilla to hand, with numbness in the forearm, and atrophy in the upper arm: there was no joint swelling: the right biceps did not react to galvanism or faradism, but there was no reaction of degeneration; there was,

however, tenderness of the muscle. The case when reported had not reached its termination. The prognosis was 'gonorrhoeal mononeuritis of the region of the musculo-cutaneous nerve'. Bernhardt claims that the case shows that degenerative atrophic conditions are not dependent upon disease of a joint.

The condition is said to be often accompanied by other nervous complications, e. g. sciatica, epileptiform tremor, and lancinating pains. Barbellion was consulted in October, 1910, by a patient who had had several gonorrhoeas, without any discharge at the time, for pains in the testicle: his general condition was bad, and he was suffering from a cough; there was an enlarged prostate but no stricture. The patient left completely cured after fifteen days' treatment for the prostatic condition, and was well for more than six months, when he returned with the former testicular pain complicated by a sciatica; and these symptoms persisted for several months. The urinary stream was distorted and diminished; but there was no stricture. On November 11, 1911, a large bougie was passed, relieving the patient from pain for three or four days; and when the pain recurred the dilations were continued. There was a little pain in or referred to the knee, but no longer in the testicle; and seven months later the patient reported that he had had no real pain again. The diagnosis was 'testicular neuralgia and sciatica'. He distinguishes this case from these which have supervened on the decline of an acute case or during a chronic one; for here there was no arthritis for several months.

The occurrence of a gonorrhoeal sciatica is too well established to be seriously questioned; but to insist upon the stage in which it appears, its unilateral or bilateral character, its occurrence in only one sex, and so forth, is to predicate conditions which the next case may upset. Many cases of sciatica may occur in patients who have suffered from gonorrhoea previously, but have never connected the neuritis with that incident. They may be treated for the nerve affection by a different medical adviser. Such cases would be eliminated from any research. Similarly, women suffering from sciatica would generally be treated for it without the possibility of making inquiry as to the existence of a gonorrhoea previously. From these two suggestions alone it is easy to see how doctrines might be established that gonorrhoeal sciatica seldom occurs in women, and in men rarely after a considerable lapse of time from the primary disease.

The safest general conclusion is to accept the existence of a gonorrhoeal sciatica, which may be bilateral or not; is often but not inevitably accompanied by arthritis; often early and trivial; probably commoner in the male, seldom coming under notice as such in the female: and that there is no conclusive evidence that the complication may not occur long after the onset and cure of the urethritis. We may go so far as to add that if we accept the theory of gonococci remaining latent in many cases for long periods and then bursting into renewed activity, it will be almost a corollary that gonorrhoeal sciatica or any other complication may similarly be lighted up at a late period. It is not necessary to comment individually upon the cases, because no case could be

made out for a denial of gonorrhoeal sciatica and, occasionally, other neuralgias, neurites, and perineurites.

The Skin.

A very interesting complication of gonorrhoea calls for passing notice, because one theory of its origin attributes it to a trophoneurosis. Marshall mentions this as Jacquet's theory, the effect being due to the action of gonotoxin on the nervous system. Chauffard and Froin describe gonorrhoeal keratosis as among the most rare skin complications, of which there had been in 1906 only three reports published in France since 1893; but they mention some fourteen in all, the first being a gonorrhoeal arthritis which developed the skin affection during treatment in hospital: viz. horny growths on the dorsum of the left toes, papillary conical elevations, yellow in the centre with a rosy areola, at first punctiform, hard, and very adherent. These reached their height in two or three days and were easily detached soon after, leaving a fresh epidermis without pus or liquid. The feet, hands, trunk, knees, and scalp may all be seats of infection; while on the soles of the feet thick plantar growths are also mentioned.

In only two cases was arthritis absent, and then the horns were three times as high, and it is suggested that they may have been due to a secondary staphylococcal infection. The horns are not always bilateral; but the plantar growths are. Chauffard and Froin consider the trophoneurotic origin as very doubtful. The pathology appears to consist in some exudative process in the Malpighian layer. The gonococcus has never been recovered from the lesion; but the affection is limited to cases of gonorrhoea. Anaemia and cachexia are usual accompaniments; and bad hygiene of the skin and irritation seem to be as essential as the primary disease. In twelve cases they did not find one with any exaggeration of knee-jerks.

Williams states that the affection occurs where there is other evidence of gonococcal septicaemia or pyaemia. Before his publication in 1910 there had been only one case in this country. He speaks of a diffuse thickening of the horny layer of the sole or transparent, yellow, horny cones or domes, chiefly on the hands or feet, but not exclusively. The excrescences can be removed in a month or two, leaving a red dry area, while the base of the horn itself is covered with a putty substance. One of his own patients was suffering from gonorrheal arthritis complicated by this manifestation.

Luys states that the keratoses occur from three to five weeks after infection and are symmetrical and almost confined to severe cases. They are described as horns, conical protrusions, and hard irregular patches, chiefly on the limbs, though they may be anywhere, including the genitals.

Sequeira describes the affection as keratodermia blennorrhagica, a symmetrical horny eruption on the soles but described also on the dorsum of the toes, occurring in gonorrhoea. He says that the first English case was described

by him in 1910, the primary disease being a gonorrhoeal arthritis with anaemia and cachexia. Along the inner border of each foot was a horny mass with a nodular surface, purple nodules like sloes being embedded in the skin and similarly along the outer border of each sole, while the intervening area was covered by a parchment-like epidermis: and there was a narrow zone of hyperaemia defining the affected area.

Gougerot and Clara, referring to the skin complication of hyperkeratosis, remark that it has been called a trophic trouble; that its existence as a gonorrhoeal manifestation appears to be beyond doubt; that Chauffard and Fiessinger consider its origin to be toxi-infectious, favoured by maceration: they describe it as a kind of dry 'hyperkeratosic pyodermity', produced by gonotoxin liberated by the dead gonococci in the lesions. They describe the case of a man, 31 years of age, who denied gonorrhoea, but in whom a stricture was subsequently found. He was also suffering from arthritis. They divided the lesions into cones and large, circinate, hyperkeratosic plaques, the latter being a horny growth without cones except around the edges, and found chiefly on the soles. Less characteristic lesions were found on the palms and arms, while there was a diffuse pityriasis on the back of the neck. They accept the affection as an established gonorrhoeal complication, and state that it has been described as a trophic trouble.

Montpellier describes the case of an English soldier, 29 years old, with gonorrhoea of a year's standing complicated by arthritis, muscular atrophy, and cachexia. Ten days after admission to hospital the patient was found to have a typical plantar keratosis. In the next fortnight twenty 'elements' were distributed on legs, thighs, palms, forearms, and trunk. Most of them were 'studded' lesions. Local treatment was purposely withheld and, in the event, two months later nothing was left of the skin trouble except a rosy surface still slightly desquamating.

Lumby insists upon the 'constant association of urethritis, arthritis, and skin lesions' in all instances of keratodermia blennorrhagica; adding that 'no satisfactory explanation of the cause of this complication has been presented', and that the only micro-organism cultivated from the skin lesions has been a staphylococcus. The affection seems to be clearly due to gonorrhoea.

Marshall refers to Landouzy's gonorrheides, attributed by some to angio-neurotic influence, by others to gonotoxin: they are macular, papular, vesicular, or scarlatiniform erythemata, and erythema multiforme. He states that Balzer has reported a case of trophoneurotic onychia, with a bullous dermatitis complicating gonorrhoeal rheumatism.

Statistics.

With the view of ascertaining whether any light could be thrown on the relative incidence of the nervous complications of gonorrhoea by an examination of the record of cases, I obtained the kind permission of the Board of Management

of our chief hospital for venereal diseases to examine the papers. It must not be expected that the result will give in definite figures the percentage of complications. Hospital records are usually far from exhaustive.

The most efficient medical and surgical officers may have the least taste for the compilation of statistics or the written record of every symptom of interest coming under their notice; the practical side of their work naturally appealing most strongly to them. And in this particular instance, the very extraordinary number of patients attending for treatment necessitates the utmost economy of time on the part of the resident staff. Moreover, the complications are in themselves elusive. A patient may apparently be cured of his gonorrhoea, and yet it is only in accordance with our experience of this and many other diseases that a latent focus may remain. The patient may afterwards become 'run down', as it is called, or may indulge in an outburst of prolonged conviviality; and the reinvigorated micro-organism may escape from some unsuspected hiding-place, such as the prostate, and enter the blood-stream. Some nervous trouble such as sciatica may follow, or something far more serious, for which the sufferer attends a general hospital and is lost sight of. If, on the other hand, the complication occurs during the early stages of the primary disease, it is more likely to be recorded; but false deductions may be drawn from such instances, e. g. that gonorrhoeal arthritis or sciatica occur at a particular stage or take a particular course.

Still the figures will at least confirm the generally accepted opinion that nervous complications of gonorrhoea are, in the main, extremely rare.

I have made some inquiries at other London Hospitals; one a Military Hospital, where I was assured that no gonorrhoeal nervous complications would be found in the records, no special attention having been directed to the subject; another a Hospital for Nervous Diseases, where no such complication had occurred within a reasonable time; while at the third, such cases had been alleged (and in some the Wassermann was negative), but the authorities had adopted the view that the safest conclusion was to ascribe such rare developments to undiagnosed or latent syphilis in the past.

It will be seen that the cases remaining for gonorrhoea with nervous symptoms are extremely small.

Syphilis.	Gonorrhoea.	S. and G.	Soft Sore.	G. and Arthritis.	Epididymitis, &c.
2,636	2,071	812	180	77	97

G. and Bartholini Abscess.	G. and Eye Complications.	G. and Nervous Symptoms.	G. and Other Complications.	Doubtful Non-venereal, &c.
54	28	22	183	605

Total 6,304.

The figures of the gonorrhoeal complications are excluded from the total, having been accounted for in the column for gonorrhoea.

The chief of the nervous symptoms mentioned were trivial. Thus nocturnal enuresis and incontinence of urine are occasionally met with, sciatica, neuralgic headache, dorsal pain, pain and heat in the legs, sexual impotence, accompanying,

in each case, gonorrhoea without suspicion of syphilis: so also genito-crural neuralgia; sometimes abdominal pain; in one case a urethral discharge for nine months with pain in the right shoulder, toes, plantar surface, and both thighs, with frontal headache. There was in this instance a vague history of a sore, but it was not treated and was apparently not suspected to be specific.

Another case was a woman, with a yellow vaginal discharge for a similar period of nine months, admitted April 28, 1917, complaining of vertebral pain in the dorsal region, with violent headaches and vertigo, for a week. Temperature 102·6° F. evening and 99° morning. She was, however, sent to a General Hospital on May 7, 1919; and it may be inferred that the final diagnosis excluded a gonorrhoeal origin.

Another woman was admitted on October 24, 1916, and discharged April 17, 1917, on the ground that nothing more could be done for her. The diagnosis was hysteria. She had a yellow vaginal discharge for six months and complained of general anaesthesia; but improved very considerably, and was completely cured of the cervicitis before leaving.

Another female gonorrhoeal patient, admitted August 29, 1918, showed mental symptoms with suicidal tendencies. The patient tried to strangle herself and threw herself from a window. She had been restless and incoherent, and complained of constant headache; and was finally transferred to a mental hospital. There is not sufficient information to show whether the mental condition was definitely traced to the gonorrhoea.

I only found one case definitely diagnosed as cerebro-spinal meningitis. This was a girl 18 years old with a vaginal discharge and venereal warts. However, she had cervical as well as inguinal adenitis on admission on March 3, 1915. Kernig's sign was present, as well as retraction. Knee-jerks were almost abolished, and plantar reflexes doubtful: no clonus or anaesthesia: negative nose and throat swabs. The cerebro-spinal fluid came very slowly on lumbar puncture. Vertigo, faintness, slight headache, and vomiting were present. After nine days temperature was 104° F. and the patient had a slight rigor. Two days later she was reported as having been delirious, but took a fair amount of food next day, when she had a slight ankle clonus. She improved steadily, and on April 19, 1915, Kernig's sign was absent, the vaginal discharge slight, and the patient could walk to the surgery. A slight vaginal discharge was still present a week later, but on May 10 she was well enough to leave hospital at her own request and refused medical examination. The notes show that the gonorrhoea and meningitis cleared up simultaneously. There is no hint as to a history of, or any treatment for, syphilis. No doubt the slight cervical adenitis suggests the possibility; but it is common enough without any such origin.

One other case is worthy of notice as a warning against a too hasty diagnosis. A man, 33 years old, attended on August 25, 1919, for recurrence of gonorrhoea. During my attendance at the clinical practice, I received a report from the patient on January 25, 1920, of numbness of the legs and anaesthesia of the feet and an 'electrical shock' from back to feet when sneezing. On

December 22 his medicine had been changed to salicylates, and, with the typical reasoning of a patient, he had attributed his new symptoms to the new medicine. The knee-jerks were excessive; and a note was taken of the nervous symptoms for further reference in case of their development. The weakness in the legs increased, and later a detailed examination and lumbar puncture were performed by Mr. MacDonagh, F.R.C.S., to whose clinic the patient had been assigned for the purpose on a subsequent attendance before the house surgeon. The clinical findings were as follows: He had his first gonorrhoea in France in July, 1917. The discharge ceased in three months, but the medical attendant would not give him a clean bill of health until a year had elapsed. In July, 1919, he had a second attack and was treated in Brussels, and later the paraesthesia, &c., supervened. A fortnight later the sensory disturbance had reached the level of the waist and was followed by increasing weakness with some backache. Patient walked with a stick, the left leg being weaker. There was no Romberg; but he felt unsteady from weakness on closing the eyes. He had always been an absolute teetotaller and never had syphilis. The only 'rheumatic' history was an attack of lumbago ten years previously. The gait was spastic: no ataxia: pupils normal: no nystagmus: nor loss of joint-sense or astereognosis: knee-jerks very brisk: slight tendency to Babinski, and on the right a slight pseudo-clonus: anaesthesia for sharp and blunt up to IX dorsal segment on the right side and XI dorsal segment on the left: motor weakness greater on the left side: no sphincter trouble, though the patient states that he had always been somewhat nervous on commencing micturition. No family history of any special kind could be elicited.

Here, then, was paralysis with predominant left motor and right sensory symptoms. A provisional diagnosis of nervous disease due to generalized gonorrhoea seemed justifiable. The cerebro-spinal fluid, however, was found to be discoloured; and the gonorrhoea having been long cured, patient was sent to hospital for nervous diseases. I followed up the case so far as to make inquiries a few weeks later, and found that a diagnosis of tubercular spinal caries had been made, based on X-ray examination, three vertebrae being clearly involved, and the nervous complications ascribed to compression paraplegia. A few weeks later the general condition was fair; but the paraplegia had not improved.

Kienboch, in his classification of gonorrhoeal arthritis, mentions a 'vertebral arthritis, with stiffness and symptoms of compression of the roots', to which category this case might have been assigned if no lumbar puncture and X-ray examination had been made.

General Conclusions.

Gonorrhoea has in all cases a tendency to produce slight psychic manifestations, which may be due to a feeble toxaemia. Obstinate chronic cases evolve neurasthenia, hypochondriasis, and a tendency to a grave melancholia. There is

some clinical evidence of a rare gonorrhoeal hysteria. Toxic delirium is not unknown, and may, with extreme rarity, develop into acute mania.

There is an appreciable number of cases in which gonorrhoea, without being itself the direct cause, has 'hatched', and so indirectly occasioned, mental disturbance.

We are prepared for the involvement of the central nervous system by Moltschanoff's experiments; and there is some evidence, from extremely few cases, however, of lesions of the central nervous system either directly from gonococcus or gonotoxin, or as a secondary effect of gonorrhoeal infection. On the other hand, a gonorrhoeal cerebro-spinal meningitis has been clinically established, and the diagnosis confirmed by some macroscopic and microscopic post-mortem evidence.

Gonorrhoeal meningomyelitis, too, though also rare, is supported by an appreciable number of cases, and established as definitely as many other rare diseases. The evidence of a multiple neuritis is less satisfactory, the clinical pictures being generally rather involved than definite. Yet we may safely assert that gonorrhoea may be charged with symptoms of that syndrome.

Minor cases of neuritis and neuralgias are relatively common; but to assign specific characteristics to such affections, when of gonorrhoeal origin, is apt to be illusory. Those special characteristics may, indeed, accompany such gonorrhoeal complications as are brought to the notice of venereal specialists; but these may be only a fraction of the cases treated.

Speaking generally, no gonorrhoeal complications can be rigidly attributed, on the basis of a convincing mass of evidence, to the primary causal organism alone; and in this, as in other infectious diseases, the obvious fact that every complication has a complex aetiology must be insistently emphasized.

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A STUDY OF PNEUMONIAS AND TYPES OF PNEUMOCOCCI

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Problems concerning the prevention and treatment of the pneumonias and their complications are still pressing for solution. When the work which forms the subject of the present paper was begun in January 1920 little had been published about the occurrence in England of the various types of pneumococci which are included in the classification of the Rockefeller Institute for Medical Research. This classification is based upon mouse-protection experiments. The sera of animals immunized against various strains are used, and it is found that doses of the same strain, which under ordinary circumstances would prove fatal, are rendered quite innocuous if closely followed by injections of the corresponding antiserum. Three 'fixed' types are thus distinguished, which can be quickly determined by macroscopic agglutination. A fourth type includes many heterogeneous strains giving no one 'fixed' antiserum.

During the past year Armstrong (1) and Griffith (2) have published their results in classifying pneumococci found in connexion with lobar pneumonia and other diseases of the respiratory tract. Logan (3) has determined the types which were found during the influenza pandemic.

It seemed of very practical importance to learn what proportion of the lobar pneumonias in England are caused by Type I pneumococcus, for in the United States the mortality in this group has been very considerably lowered by intravenous treatment with specific antiserum. Thus Cole (4) reports a death-rate of only 10·5 per cent. in 495 cases of Type I lobar pneumonia treated at the Hospital of the Rockefeller Institute and in other hospitals of the United States. The rate of mortality in America amongst such cases, when not treated with specific antiserum, lies between 25 and 30 per cent. When one considers that about one-third of the cases of lobar pneumonia in the United States are caused by Type I, then it is realized how important this work has been.

In this present study material from cases of broncho-pneumonia and from

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other sources was deliberately chosen at times when no fresh cases of lobar pneumonia were to be found in the hospital. For the most part, however, the bacteriology of the latter disease has been studied. The results of the work, therefore, show the relative incidence during the last year and a half at one hospital of various types of pneumococci in lobar pneumonia. The figures are of little importance in determining the relative frequency of lobar and broncho-pneumonia. This last question is not unimportant, for it struck the writer in France during the war that amongst adults of military age there were more cases of broncho-pneumonia in proportion to those of the lobar variety than one was accustomed to see in Canada. Such an idea was entertained before the influenza pandemic. Then, again, some physicians are of the opinion that in proportion there are not so many cases of lobar pneumonia now as there were ten or twenty years ago.

The cases have been studied clinically as well as bacteriologically so that an account might be kept of the complications as they arose in pneumonias caused by the different types of pneumococci.

Methods of Determining the Types.

As rapid a method as possible should be employed to determine the type of organism if we hope to use antiserum in the treatment of lobar pneumonias in this country. The sooner treatment is commenced the more chance is there that it will prove beneficial. And again, many of the patients have already been ill for several days before they are admitted into a general hospital. The average duration of disease before admission was 4·3 days in the case of fifty-three lobar pneumonias.

Urine precipitin method. The most rapid method at present in use is the urine precipitin one devised by Avery and Dochez (5) in 1917, and now employed in many hospitals in the United States as part of the routine examination in all cases of lobar pneumonia. In the growth of a pneumococcus a soluble substance is produced which is precipitated by the specific immune serum which has been prepared by inoculating an animal with the corresponding type of pneumococcus. Dochez and Avery have shown that this specific substance is excreted in the urine of patients suffering from lobar pneumonia. In some cases it could be detected as early as twelve hours after the initial chill. This method is excellent if it gives a positive result, and confirmation will follow if cultures are made from the sputum and the organism isolated. There are drawbacks, however, as it has been ascertained that the precipitable substance is found in only about 65 per cent. of cases of lobar pneumonia due to three 'fixed' types, i. e. Types I, II, and III. Thus, if a negative result is obtained one does not know whether the case lies amongst the remaining 35 per cent. of the pneumonias caused by the 'fixed' types or is caused by a Type IV organism, for the various strains of which there is no 'fixed' antiserum. Another disadvantage is that larger amounts of antisera are required for the precipitin test than for agglutina-

tions. In the present instance the supply of antisera at the writer's disposal was not large, and the test was employed in nine cases of lobar pneumonia only. On four occasions it was positive for Type I, twice it was the only test carried out, and on the other two occasions the result was confirmed by agglutination of the isolated organism. In another case where the agglutination was positive for Type I, the urine test was negative. In three cases of Type II lobar pneumonia as determined by agglutination, the urine precipitin test was positive in one instance and negative in two. The precipitin test was negative in a case of lobar pneumonia in which the agglutination showed Type III.

Rapid cultural method. The next most rapid way of learning the type was described by Avery (6) in 1918, when the supply of mice for the original method was scanty. A special meat infusion broth, containing 1 per cent. glucose and 5 per cent. defibrinated rabbit's blood, is inoculated with a kernel of sputum which has been washed several times in sterile normal saline. This medium produces a luxuriant growth of pneumococci after five hours' incubation at 37° C., but a minimal one of other organisms. The precipitable substance produced by the growth of the pneumococci is extracted with bile, and the precipitin test carried out with the three antipneumococcal sera. The result may be confirmed by isolating the pneumococcus from the sputum by inoculating a mouse. This method was made use of several times, but unless one can always arrange to get the sputum in the morning, or unless one lives in the hospital, it is difficult to carry out the test.

Mouse method. The method employed by the writer in the vast majority of cases has been the original one as used at the Rockefeller Institute. The peritoneum of the mouse is a splendid medium for the pneumococcus, and a rich growth may be obtained overnight. It is important to obtain the sputum from as low down in the respiratory tract as possible to avoid contamination with organisms of the naso-pharynx and mouth. It is also of importance to collect the sputum oneself or issue implicit instructions. The patient is made to gargle several times and wash out his mouth with warm water, and then induced to cough and spit directly into a Petri dish. In the laboratory the sputum is washed several times with normal saline and a small portion of it worked up into an emulsion in sterile broth with a pestle and mortar. One-half to 1 c.c. of this emulsion is now injected into the peritoneum of a mouse. As a rule the animal dies overnight or becomes very ill. In either case a drop of peritoneal fluid is obtained with a very fine capillary pipette made by drawing out glass tubing. Smears are made and stained with His's capsule stain and by Gram's method. The capsules show up very distinctly. If the organisms are scanty, and form merely circles about the numerous cells of the peritoneal exudate, more time for growth is required and the animal must be left for several hours. Otherwise an autopsy is performed at once (killing the animal with ether or chloroform if necessary), cultures being made from the peritoneum and heart's blood on blood agar and in broth. Generally there is little free fluid in the peritoneum, but by washing the cavity with sterile saline, using about a cubic centimetre at a time, 15 c.c.

or so of very turbid fluid may readily be obtained. This of course contains many cells and some fibrin, which can be thrown down by centrifugalizing slowly. The supernatant fluid is then very rapidly centrifugalized in another tube and the pneumococci thrown to the bottom. An emulsion of these is then made up with saline to the required strength. Agglutination tubes are set up with the antisera, using dilutions recommended for the particular sera. After standing in a water-bath at 37° C. for one hour, the agglutination, if present, may be read off with ease, as a tenacious white disk lies at the bottom of the tube. Bile solubility tests, using four drops of sterile filtered ox-bile and sixteen drops of the emulsion of pneumococci, and control tubes, are also made, and read after half an hour in the water-bath. Not all strains of pneumococci do ferment inulin, but this test was sometimes used as a confirmatory one. If the organism is a Gram-positive diplococcus possessing a capsule and is soluble in bile, but does not show agglutination in any of the three 'fixed' types of antisera and also produces characteristic growths on blood agar, it is considered as a pneumococcus belonging to the heterogeneous Type IV. In some cases of empyema a mouse was inoculated with the pus, and chains of Gram-positive cocci, which had no capsule, were seen in the peritoneal fluid, were not bile soluble, and showed no agglutinating properties with the three sera. Colonies generally distinguishable from pneumococcal ones were obtained and the organism was regarded as a streptococcus.

No attempt was made to subdivide Type IV, as this can be done only by immunizing a separate rabbit with each strain and then carrying out cross-agglutination tests. Olmstead (7) has shown by this method that at least twelve distinct strains exist. These are the strains that are most commonly found in the throats of normal people, but they may cause lobar pneumonia having a very low death-rate.

If the patient was a child or for some other reason did not expectorate, the mouth and pharynx were cleansed as well as could be with warm water and the patient induced to cough on to a sterile swab thrust back into the pharynx. The cotton-wool of the swab was worked up in broth with a pestle and mortar and a mouse inoculated. A direct smear from another swab was examined and the kinds of organisms noted. If pus from an empyema was used for inoculation of the mouse, it was first diluted in a mortar with a little broth. Sometimes a portion of hepatized lung was emulsified in the same manner, and this method was preferred to that of taking cultures of the contents of the large bronchi.

Cases of Lobar Pneumonia.

Incidence of the types. Sixty-seven cases in all of lobar pneumonia were studied. There were 24 due to Type I, or 35·7 per cent. Twenty-four were due to Type II, or 35·7 per cent. of all cases. Two cases were caused by Type III, or 2·9 per cent. Seventeen cases were due to Type IV, or 25·4 per cent. of all the cases. Doubtful cases have been excluded as far as possible and put in

amongst those of broncho-pneumonia. Griffith's recent paper (2) gives the following percentages; Type I, 24; Type II, 35; Type III, 10; Type IV, 31. The most marked difference is seen in the incidence of Type III cases. It must be noted that his material came from several hospitals and infirmaries, and it would be interesting to learn whether his Type III cases occurred in little groups from different areas.

The Rockefeller workers (8) found that in their first hundred lobar pneumonias the percentages were: 33, 33·5, 13, and 20·3.

In fourteen of the writer's cases the Type II organism belonged to one of the subgroups, as agglutination took place in undiluted Type II serum only. Stillman (9) has distinguished twelve of these 'atypical' groups.

Mortality. Four of the Type I patients died, a mortality of 16·7 per cent. in this group. The death-rate in the Type II cases was 37·5 per cent., as nine patients died. Neither of the Type III patients died. There was only one death amongst the Type IV patients, or a death-rate of 5·9 per cent. Apparently in the United States the mortality in lobar pneumonia due to the four different types is about 25, 32, 45, and 16 per cent. In considering, as a practical question, the number of cases available for treatment with specific serum perhaps the writer should have included two cases of Type I septicaemia with peritonitis; some patchy pneumonia in one case, and pericarditis and empyema in the other. Both these cases were fatal. If they were included with the above the death-rate would be 23 per cent. The difference in the death-rate in the Type III cases of the present series and in the United States is very striking. Both of the cases noted here had a fall of temperature by crisis, on the tenth and seventh day of illness respectively. Either it was just a matter of chance that the two cases seen were mild ones, or the Type III pneumococcus concerned belonged to one of the strains that are found in the mouths of healthy persons (10) which perhaps at times do not cause a malignant form of lobar pneumonia. It may well be that the general mortality-rate in the British Isles or Europe is not as high as in North America. The present writer had 104 cases of lobar pneumonia under his care from August 1917 to August 1918 in France, excluding any influenzal cases, and there was a mortality of only 18 per cent. No serum treatment was used.

Epidemiology. The figures here presented are not large, but they go to show that from month to month the type of organism causing the majority of lobar pneumonias may change, as Nobécourt, Paraf, and Bonnet (11) have shown to be the case in France. For instance, during the winter of 1921 marked differences were noted in the months of February, March, and April, in which months the number of cases due to Type I were six, one, and four; to Type II, nil, six, and one; to Type III, nil, nil, and nil; to Type IV, three, three, and one respectively.

The two cases of Type III lobar pneumonia were admitted within two days of each other in July and August 1920.

It might be well as a piece of Public Health work to carry out in this country such studies as those of Dochez and Avery (12) and Stillman (10), (13)

upon the epidemiology of pneumococcal infections, including the question of carriers and that of infection from person to person.

Pfeiffer's bacillus in the lobar cases. This was seen in the direct smear of a throat swab in two cases of Type I lobar pneumonia. In one of these it grew out in the peritoneum of the mouse, and in the other only on a blood-agar plate inoculated with the throat swab.

In one case due to Type II, Pfeiffer's bacillus grew out in the peritoneum of the mouse inoculated with the sputum. In another case the peritoneum of a mouse, inoculated with an emulsion of hepatized lung, showed Pfeiffer's bacillus as well as a Type II pneumococcus.

In the Type IV lobar cases Pfeiffer's bacillus grew out four times in the mice used; three times when inoculated with sputum, and once when inoculated from a throat swab.

It is of interest to note that Pfeiffer's bacillus was more often found intimately associated with Type IV than with Types I or II, which are not so often isolated from throats of normal persons.

Complications due to the different types. Amongst the twenty-four Type I cases, nine had *empyema*; two patients died and one of them also had pericarditis. There were four cases of empyema amongst the twenty-four cases due to Type II, and two of these ended fatally. The two Type III patients showed no complication and recovered. Four of the seventeen Type IV patients had empyema and only one of these died.

Only one of the sixty-seven lobar cases was complicated by *pericarditis*—a case caused by Type I which also showed empyema and ended fatally.

One patient with Type IV lobar pneumonia also had *endocarditis* found at autopsy. He was about forty years of age and died on the sixth day of disease. There was grey hepatization of the left lower lobe and a large turbid pleural effusion on the same side. In the right upper lobe there was some bronchopneumonia. The aortic valve had only two cusps and there was old as well as recent endocarditis on both aortic and mitral valves. A Type IV pneumococcus was isolated from both consolidated lung and endocardial vegetations which were washed in sterile saline and emulsified in sterile broth.

In a fatal case of Type I lobar pneumonia, which occurred outside the hospital, there was a complicating *meningitis* caused by the same organism. In a case of Type I lobar pneumonia *acute nephritis* arose. The only instance of true *massive pneumonia* of the whole series was in a fatal case due to Type II. It was diagnosed clinically. The cut surface of the lung showed plugs in all the bronchi except the very largest, and suggested beginning abscess formation here and there. This idea was confirmed microscopically, and Dr. Spilsbury also noted delayed resolution and commencing organization in some areas.

That empyemas in lobar pneumonia are generally caused by Type I is borne out by the above findings, and also by those of Thomas and O'Hara (14), who report that amongst the first thirty-one cases of pneumococcal empyema they investigated, 20, or 60 per cent., were due to Type I. They consider that this

organism is very apt to invade the blood-stream. It may be noted that the cases of pericarditis and meningitis described above were also caused by Type I. Below will be given some instances of peritonitis due to the same type.

Little has been written about the types of pneumococci which cause endocarditis. Wadsworth (15) described the endocardial lesions which are sometimes found when horses are inoculated to produce anti-pneumococcal sera. He reports five cases due to Type I, one due to Type II, one due to Type III. Thomas and O'Hara (14) describe a case of Type I tricuspid endocarditis in a fatal case of Type I lobar pneumonia. They have reviewed the literature and show that in man four cases were caused by Type I, none by Type II, one by Type III, and one by Type IV. The case above gives another to Type IV.

Cases of Broncho-pneumonia.

As stated above, those cases which were not definitely lobar in character were classified as broncho-pneumonic. Two cases were due to Type I. Both patients had empyema and recovered. In one instance the organism was also obtained from the sputum. It is of interest to note that Pfeiffer's bacillus did not grow out on blood agar on which the washed sputum was cultivated, nor did the peritoneal exudate of the mouse, which had been inoculated with the same material, reveal the presence of this organism.

The pneumococcus from five cases of broncho-pneumonia belonged to Type II. One patient died and the organism was isolated from emulsified lung by inoculating a mouse. None of these cases showed empyema or any other complication. Pfeiffer's bacillus was seen in three of the mice used.

Type III pneumococcus was isolated from two cases of broncho-pneumonia. One was a fatal case in a very large man forty-four years of age. All through his illness he was very dyspnoeic and cyanosed. He brought up large quantities of greyish-green, purulent, nummular sputum. There was no dullness on percussion but signs of a generalized bronchiolitis. Here and there over small areas the breath sounds were decreased. Bubbling râles were heard over the large bronchi. A direct smear of the sputum showed many polymorphs, many fine Gram-negative bacilli, some Gram-positive diplococci with large capsules, and also a few Gram-negative intracellular diplococci. A blood-agar plate was inoculated and, when examined twenty hours later, typical pneumococcal colonies were found. After another day, hundreds of tiny colonies, characteristic of Pfeiffer's bacillus, had grown out and smears showed many fine Gram-negative bacilli with many involution forms. A mouse had also been inoculated with washed sputum and was almost dead when seen seventeen hours later. The peritoneal exudate showed many Gram-positive diplococci possessing very large capsules and very many Pfeiffer's bacilli. It was thought unwise to attempt agglutination with such a mixture, but blood-agar plates were inoculated with peritoneal exudate and heart's blood and both kinds of organism grew out.

Another mouse was inoculated with an emulsion of two colonies of the pneumococcus and the animal died some time between twenty-four and thirty-six hours later. Agglutination was performed and was positive for Type III only.

This patient died after an illness of about two weeks, by which time the sputum had lost something of its nummularity. No signs of gross consolidation were detected before death. No autopsy was permitted.

The other case was of a man, 20 years of age, who had a small patch of consolidation in the right lower lobe. The sputum was not nummular, but direct cultivation upon blood agar produced a growth of some fine colonies of Pfeiffer's bacillus and many ringed colonies of pneumococci with a zone of slight haemolysis about them. From a mouse pneumococci were recovered and agglutination was positive for Type III only. A few colonies of Pfeiffer's bacillus also grew out from the peritoneal exudate and heart's blood of the mouse. There was no associated general bronchiolitis and the patient recovered.

In eleven cases of broncho-pneumonia a Type IV pneumococcus was recovered from the sputum or empyema pus. Four of the patients died, and three of these had empyema caused by Type IV. In one fatal case the organism was identified by inoculating a mouse with an emulsion of hepatized lung. Pfeiffer's bacillus was also isolated from the sputum of eight of the patients and once from empyema pus.

The most striking thing about the cases of broncho-pneumonia is that in the majority a Type IV pneumococcus is found, a type which has been shown to be saprophytic in the throats of many people. Closely associated with the pneumococcus (Type IV) is Pfeiffer's bacillus, and it is difficult to assume that this latter organism does not play a part in the disease.

Before the bacteriological examination was made in the former of the Type III cases, a preliminary diagnosis of bronchiolitis and broncho-pneumonia due to Pfeiffer's bacillus was given, for the aspects of the patient, the sputum, and the physical signs closely resembled those of a series of nine fatal cases recently described by the writer and Rhea (16). The abundance of Pfeiffer's bacilli subsequently cultivated from the sputum make it most probable that this organism was the cause. Although it is more common to find a Type IV pneumococcus with the *B. influenzae* of Pfeiffer, it is probable in this case that the patient was a carrier of Type III. In the series of fatal cases referred to above, although Pfeiffer's bacillus was the only one seen or cultivated from the finest bronchi (where the lesion lay), pneumococci and other organisms were cultivated from the contents of the larger ones, and here the flora closely resembled that of the sputum.

In the latter case, where a Type III pneumococcus was isolated, it seems most likely that, as Pfeiffer's bacilli were not found in great abundance and the signs were not characteristic of a Pfeiffer infection, the pneumococcus was the cause of the pneumonia.

Pneumococci from other Sources.

In the sputum of a young woman two weeks after the onset of acute tuberculous broncho-pneumonia a Type I pneumococcus was present together with tubercle bacilli. The illness began suddenly with a profuse haemoptysis, but without a chill or sharp pleuritic pain. Soon after the onset, herpes appeared on the lips. Her temperature was more irregular from the first than is commonly the case in lobar pneumonia. On admission there was consolidation of most of the right upper lobe; this gradually spread and she died at the end of about two months. No autopsy was obtainable. The illness was probably tuberculosis from the start, but it is not common to find a Type I pneumococcus in the sputum of a person who has not got a pneumococcal infection. In another case of extensive tuberculosis of the lung with tubercle bacilli in the sputum a Type IV pneumococcus was isolated.

Peritonitis. Four cases in all were investigated. Two cases were of generalized pneumococcal septicaemia in young children. A little girl was admitted on the fourth day of disease with signs of a generalized peritonitis, signs suggestive of pneumonia of the right base, and herpes labialis. She was operated upon but died the following day. At the autopsy there was bilateral pleurisy, some patches of broncho-pneumonia, haemorrhages into the suprarenals, and general peritonitis. The other case was in a small boy who died on the tenth day of disease. At the autopsy there was found peritonitis, as well as 'bread and butter' pericarditis, and a turbid pleural effusion on the left side with great compression of the lung. The two other patients were adults; both were operated upon and recovered.

There are few references in the literature to the type of pneumococcus found in such cases of peritonitis. It is interesting to note that Type I was the cause in all the four cases recorded above, for it has been shown to be a frequent invader of the blood-stream, and an antiserum has already proved its worth in the treatment of pulmonary affections caused by this type. In a discussion of Syms's paper in 1919 (17) on pneumococcal peritonitis, Lambert relates that a female child, whose father had Type I lobar pneumonia, was admitted to hospital with Type I peritonitis and was operated upon. The nurse caring for her also got Type I peritonitis and was operated upon. Both child and nurse were also treated with Type I antiserum and, although in both a Type I post-operative pneumonia developed, both recovered. In the same discussion Whipple reports three cases due to Type I. Recovery followed operation and specific serum treatment. Another of his cases due to the same type was of the diffuse form of peritonitis and quickly proved fatal. These results, together with Koennecke's account (18) of twelve recoveries in twenty-seven cases seen from 1908 to 1918 at Göttingen, show that pneumococcal peritonitis is by no means always fatal in children or in adults. No antiserum was employed in Koennecke's cases; the total mortality was 55 per cent., but only 45 per cent. if five cases of general pneumococcal septicaemia are excluded.

Meningitis. In one man, 69 years of age, middle ear disease was complicated by meningitis. A pneumococcus was found in the cerebro-spinal fluid during life. After death a Type III pneumococcus with very large capsules was isolated from the meningeal exudate. This type produces a sticky mucoid growth on artificial media and sticky exudates in animals or man. It is bile-soluble, but otherwise very like *Streptococcus mucosus capsulatus*, which has so often been found in middle ear disease.

Bronchitis. In the sputum of two patients who had bronchitis but no broncho-pneumonia, a Type IV organism was found—the most common throat pneumococcus.

Subcutaneous abscess. In a young woman who had had recurrent attacks of tonsillitis and cervical adenitis, some bronchitis, and multiple arthritis, a swelling appeared over the right wrist. Mr. Gask incised this and obtained thick creamy pus, but it came from a subcutaneous abscess only which did not communicate with the joint. A mouse was inoculated and a Type IV organism isolated.

Summary.

1. It is important to collect data about the incidence of the types of pneumococci in England, and about the death-rates in the various groups of lobar pneumonia, so that later, if antiserum treatment is introduced, the results may be studied critically.

2. Questions of epidemiology, such as that of healthy carriers of 'fixed' types, the occurrence of small epidemics of lobar pneumonia due to one type, and the seasonal variation in the number of cases of lobar pneumonia due to certain types, should be answered.

3. The 'urine precipitin' and 'rapid cultural' methods are valuable in the rapid determination of types, but by the former method alone the type cannot always be determined. The most satisfactory is the mouse inoculation method, in which the agglutinations can be done after about twelve hours.

4. In the sixty-five lobar cases studied at one hospital the proportions of the different types were similar to those in America, except that much fewer of Type III were found, and more cases were due to a typical Type II subgroups. Griffith, collecting sputa from a number of hospitals, has recently recorded nearly as many cases due to Type III as in the United States.

5. At least one-third of all the lobar cases in this country are due to Type I, in which group specific antiserum has proved of benefit elsewhere.

6. The death-rates in all but Type II cases were lower than in America.

7. More complications were caused by Type I than by any other, but one case of endocarditis due to Type IV is described.

8. The three 'fixed' types were isolated from the sputum of cases of broncho-pneumonia, but more often a Type IV pneumococcus was found—the commonest throat pneumococcus.

9. Pfeiffer's bacillus may grow out in the mouse or on blood agar inoculated with washed sputum of pneumonia cases, but it was found much more often in association with Type IV, in both lobar and especially in broncho-pneumonic cases, than with the other types.

10. One of the cases in which a Type III pneumococcus was also found—a case of bronchiolitis and broncho-pneumonia—was probably caused by Pfeiffer's bacillus.

11. Type I was isolated from cases of pneumococcal peritonitis; twice in fatal cases in children, with the generalized septicaemic form; and twice from adults (with no septicaemia) who recovered.

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STREPTOCOCCAL INFECTIONS OF THE HEART

By CAREY F. COOMBS[1]

Introduction.

This report summarizes briefly histological investigations which began in 1906 and have continued since, except for a long interruption caused by the war. Their main purpose has been to throw light on the aetiology of rheumatic carditis, and my reason for publishing a report at this juncture is that it seems possible to state certain deductions which may be of use to those who are interested in this problem from various points of view. Some allusion is necessarily made to the researches of others, but the report is primarily an account of personal investigations and opinions, and therefore includes (for reasons stated on pp. 119–120) among the lesions caused by streptococcal infection those of 'rheumatic' carditis.

Part I.

'Rheumatic' Carditis.

The work began on this wise. In 1906 or 1907 an autopsy on a boy under my care at the Children's Hospital, Bristol, impressed me as nothing had before with the overwhelming importance of the myocardial lesions of acute rheumatic carditis. Further observation confirmed this impression, and led to a careful study of the histological changes accompanying the failure of myocardial function. These were fully described in 1907 and 1908 (1). Apart from fatty change not much was found within the myocardial cells, and even this was not as pronounced as one might have expected. But the interstitial changes were very remarkable. The first detailed account of these phenomena was published by Aschoff (2), who described them as 'submiliary nodules', and associated them with rheumatic infection. Seven or eight years before, Poynton (3) had published pictures illustrating similar myocardial foci in rheumatic carditis, but without a detailed account of their peculiar features. Since Aschoff's paper in 1906 various observers have confirmed the principal points reported therein.

For convenience' sake I reproduce here a brief account of the nodule written by me in a former paper (4):

'The nodules consist of a groundwork of fibrin, surrounded and interrupted by various cells. Of these, the most important are certain large cells which

[1] A Report to the Medical Research Council.

form the characteristic feature of the nodule; there are also leucocytes and plasma cells. The nodule varies in shape: sometimes it is globular, sometimes spindle-shaped, possibly according to the plane in which it is cut, also according to the pressure exerted by the surrounding tissues. For instance, the nodules which lie in the interstices of the cardiac muscle are long and spindle-shaped; in other positions they are more likely to be rounded.

'That the groundwork consists of fibrin is shown by its appearance, a "fine, fibrillary matrix", such as I described in a former paper, and by its staining reactions as tested by various methods. In the myocardial nodules the fibrin is often obscured by the cells, which are crowded together by the narrowness of the limits within which the nodule has developed. Even here, however, there is a background of fibrin, and within spaces in its midst the cells seem to fit. The pericardial and endocardial nodules have more room; in these there is often a central area consisting of nothing but fibrin, surrounded by a zone of cells either mingling with the fibrin at its margin, or marking it off from the surrounding tissues. Usually the fibrinous patch has a definite edge and does not fade off from the neighbourhood of the nodule.

'The characteristic large cells vary a little in shape according to the shape of the space in which the nodule develops: in rounded nodules the cells are often globular, but even in such they may be fusiform, and this is the form they tend to take. That they are soft is shown by their taking shape from one another as to give flat sides and quadrilateral outlines to each. The largest cell is of such a size that, measured from pole to pole, it is equal to a third or a quarter of the diameter of the microscope field as seen with 1,000 magnification. Its cytoplasm, which is very finely granular, takes both basic and acid dyes readily, so that the cell is a dark object in the field. In some the cytoplasm looks opaque and the cellular outline is apt to be globular; such cells are probably being destroyed by toxins, perhaps by those which call them into being. There may be as many as seven nuclei in one cell, apparently without any definite plan of arrangement; though as many of the cells are so narrow that they can carry but one nucleus abreast, they lie in a sort of chain along the long axis of the cell. The chromatin thread of the nucleus stains sharply with haematoxylin; each nucleus appears as a space bounded by a thin black line and clear centrally except for several sharp black dots which represent cross-sections of the chromatin thread. Consequently, in a deeply-stained cell, there is a very striking contrast between the almost clear nucleus and the dark cytoplasm.

'The other cells, plasma cells and leucocytes (mononuclear, largely) which enter into the constitution of the nodules, do not need detailed comment, as they are in no way special to rheumatic lesions.'

The chief interest in the study of rheumatic infection is the discovery of its cause. To this search the nodule appeared to afford a clue, and it was with this end in view that I followed it up. In all, thirty-seven hearts from patients with rheumatic infections have been examined. In twenty-six instances, the patients were children or adolescents with manifestations of active infection. In eighteen

of these cases the myocardium was found to show submiliary nodules; of the remaining eight, three were imperfectly examined, two were cases of children dying of chorea, and three showed focal lesions which represent an early phase of the process that leads later to the formation of nodules. Eleven of the thirty-seven hearts were from patients dying of the mechanical effects of rheumatic heart affection (the type of case that is usually labelled 'mitral stenosis', 'adherent pericardium', and so on; attention being directed mainly or exclusively to some one or other of the after-effects of the infection). A majority of these patients were adults. No submiliary nodules were found in any of them. It seems fair, therefore, to conclude that these lesions are constantly associated with the active phases of cardiac rheumatism, and as constantly absent from the later cicatricial stages of the same disease.

Examination of a number of hearts from patients dying of various infections failed to discover lesions of this kind in the myocardium. From this statement there are two reservations: first, in two cases of carditis complicating scarlet fever were found lesions apparently identical with those of rheumatic carditis. In one case the identity was absolute: this boy had had an illness some time before the scarlet fever, which might have been a mild rheumatic infection. In the other case, the myocardial lesions were like those referred to above as constituting an immature phase of the submiliary nodule. The second reservation applies to certain cases of 'subacute bacterial endocarditis'. In these, inflammatory foci are occasionally found in the heart which bear some resemblance to early phases of the rheumatic process. But apart from these two exceptions, scarlatinal carditis and subacute bacterial endocarditis, the one probably and the other possibly related to rheumatic carditis, it is true to say that no infection produces inflammatory spots in the myocardium similar in character or in number to those of rheumatic carditis.

Other rheumatic lesions. The next point was to determine whether the rheumatic infection attacking other tissues than the myocardium excited a reaction similar to that which has been described above. The cardiac valves and mural endocardium, the pericardium, the joints, periarticular tissues, and subcutaneous nodes, the brain and meninges, and other tissues such as the kidney and thyroid gland were therefore examined in a number of cases. From these examinations several facts emerge. First, lesions similar in essentials to those found in the myocardium are also met with in the pericardium and endocardium in rheumatic carditis. In both they are less distinctly circumscribed than in the intermuscular planes, but this is due to their anatomical environment. Second, there is a general agreement between the intensity of the lesions found in the three layers of the cardiac wall. If there is widespread pericarditis and inflammation of several valves many intramuscular nodules will be found. If, on the other hand, evidences of inflammatory reaction are hard to find in one layer of the cardiac wall, the chances are that the same will be true of the others. (Broadly speaking, also, a heart that shows an early phase of the submiliary nodule will also exhibit early phases of endo- and peri-carditis. This

last generalization must not, however, be pushed so far as that preceding it.) Third, a comparison with other rheumatic lesions, particularly the subcutaneous node and the inflamed joint, discovered in the latter the presence of foci similar in essentials to those of the myocardium.

Evolution of rheumatic lesions. Now it was impossible to study these various phenomena of rheumatic infection without arriving at some conclusions as to the manner in which they had evolved. These conclusions may perhaps be stated in the terms of a paragraph from an article (5) by me written in 1913:

'The stages of the tissue reply to irritation by the *Streptococcus rheumaticus* would appear to be as follows: First, the endothelia of the smaller blood-vessels and lymphatics proliferate: this is manifested in partial or complete occlusion of vessels with or without thrombosis in the dissemination of "endothelial leucocytes" which are mainly collected in perivascular foci, and in the building up of new capillaries. Second, the perivascular connective tissues display a fibroblastic reaction, especially around the newly-formed capillaries. Third, leucocytes arrive in the disturbed area: in most areas the polymorphonuclears are represented but sparingly, but the more severe the attack, the more likely they are to appear, and in some spots they even dominate the picture, especially where large vessels are closed by inflammatory thrombosis. The usual appearances, therefore, are those of a blood-borne infection of a virulence so moderate that it is for the most part dealt with successfully by the first line of defence—the vascular endothelia.'

To this must be added a word as to the position of the submiliary nodule in this evolution. The nodule in its most characteristic form is a late stage, a stage so to speak of healing. The leucocytes have disappeared, and what is left is the vascular core of the lesion—a thrombotic basis of fibrin interrupted by proliferating endothelial cells and surrounded by a zone of fibroblasts. The large multinucleated cells represent a phase of the endothelial proliferation. They are derived from endothelial cells lining small blood-vessels and lymphatics. Every stage in this derivation can be traced in sections of the tissues. As this in its turn melts away it leaves but little scar.

It may be asked, How do you reconcile the statement that this lesion marks an early stage of healing with the fact that the patient dies in this stage? The reply is, I think, that he dies of the effects of the toxin liberated at the time when these lesions are being established. Not necessarily liberated from the lesions themselves, for the intracellular changes in the cardiac muscle are not very closely limited to the immediate neighbourhood of the inflammatory foci. But it is at the time when these lesions are being built up that the toxins are being formed and diffused, and their lethal effects will probably not be manifested for some days. That, at all events, appears to be the rule: the destructive action of bacterial toxins, even when they are as intense as they are, for instance, in the case of tetanus, takes time before it brings the tissue attacked to a final break-down of function.

The myocardial foci do not seem to leave much scar tissue behind. It is, of course, otherwise with the lesions of the pericardium and valves. At the height of these developments the formation of new fibrous tissue is on a far larger scale in these structures than in the myocardium. Indeed, the degree to which the myocardial foci interfere with function, even during their height, is apparently not great. Parkinson, Gosse, and Gunson (6) found that in a series of fifty cases of rheumatic carditis, all of them of the 'in-patient' degree, only four manifested interference with *a.-v.* conductivity sufficient to cause dropping of beats. Their observations of these and less definite degrees of interference with conduction suggest also that the life of these foci is short, since the perversion of function endured for periods varying from one to eighteen days only. This is closely parallel with the life-history of the subcutaneous node, and probably gives a true idea of the time occupied by the evolution and involution of the myocardial foci.

It seems therefore that each active phase in a case of cardiac rheumatism must consist of a brief but sharp attack upon the tissues of the heart, muscular and serous alike and together, by a *materies morbi* which enters those tissues by the one avenue common to them all, namely, the coronary arteries and their branches. Only in this way can we account for the prominent part played by these small vessels in the earlier stages of the focal lesions described above.

Evolution of rheumatic lesions: further considerations. How much further can these histological studies help us in our search for the exciting cause of rheumatic carditis?

(1) They serve to confirm the view that is now universally held, namely, that cardiac rheumatism is a result of a bacterial infection. The changes in the cardiac wall display all the characteristics of reaction to irritation by the toxins of bacteria: cellular proliferation with exudation of leucocytes, and alterations (of which the most obvious is fatty accumulation) within the myocardial cells.

(2) The distribution of these lesions suggests that the bacteria themselves, and not merely their toxins, enter the cardiac tissues. If it were otherwise we should expect widespread intracellular changes, with little or no interstitial reaction; and that little spread uniformly throughout the heart, not scattered about in sharply limited foci of intense inflammatory reaction.

(3) My own researches have failed to disclose visible bacteria in these lesions. Poynton and Paine (7) allude to the difficulty they found in demonstrating their organism in human cardiac lesions, and it may be that my failure is due to imperfect technique. But even if they are not easily demonstrable, it is possibly because they have been disposed of by endothelial phagocytosis before the stage at which death usually occurs—that of myocardial break-down due to diffusion of toxins—has been reached. In a case in which I failed to find them in the myocardial lesions, organisms which I believe to be causal were grown in pure culture from the pericardial fluid, so that they must have been in the tissues of the heart at the time when the submiliary nodules were being formed.

(4) There is an apparent discrepancy between this proposition—that the

bacteria die out quickly in the tissues which they attack—and the fact that active rheumatic carditis is often a quickly fatal disease. Two hypotheses may be advanced in explanation. First, it is possible that the organisms, though entering the cardiac tissues themselves, are also powerfully reinforced by toxins manufactured at some point outside the heart, whence they are poured into it with its coronary blood.[2] Second, it is possible that the organisms gain their power to kill by some process acting immediately before their entrance into the cardiac tissues and conferring on them a transient intensification of virulence.

(5) There are therefore, it seems to me, good reasons for believing that rheumatic carditis is due to the entry into the cardiac tissues of pathogenic organisms. The rapidity with which the lesions develop and die off into quiescence is against any belief in a lingering of this infective agent within the cardiac tissues, between the active phases by which the progress of the disease is punctuated.

(6) Where, then, do the organisms live during the quiescent periods which separate those active phases? It is hardly likely that they re-enter the body at each fresh outburst, for these latter occur so frequently in many instances that it is inconceivable that each of them represents a visitation of the body *de novo* from without. Presumably, therefore, they inhabit some part of the body from which they have access to the circulation without being actually within it except during the active phases. There is only one piece of evidence that gives us any clue to the precise part concerned, and that is the frequency with which an attack of tonsillitis can be shown to have preceded the actual manifestations of rheumatic infection. In such cases it seems likely that the micro-organisms were living, if not actually in the tonsils, at all events within easy reach of them.

Evidence for the coccal theory of rheumatic infection. And this brings us to a consideration of the various theories that have been advanced in regard to the bacteriology of cardiac rheumatism. Of these, only one can be said to have received any general support. It was in 1900 that Poynton and Paine published their first paper (8) on the aetiology of rheumatic fever. In this they gave a brief account of the work done by other bacteriologists up to that date, following this with a description of their own results. In those, as is well known, they claim to have isolated a small diplococcus similar to that already described by Triboulet and Wassermann.

The papers that have been written on the subject since that time fall into three groups. First, Poynton and Paine published a number of papers (9) in which they brought forward further evidence in support of the streptococcal theory. Second, other bacteriologists confirm their work. Among these should particularly be mentioned Beattie (10), Ainley Walker (11), and Rosenow (12). Third, a number of writers have criticized the streptococcal theory: some, like Bulloch (13),

[2] Paragraph (2) immediately above states an argument against this hypothesis.

on the ground that they have failed to find the diplostreptococcus of Poynton and Paine, others, such as Horder (14), on the ground that the organism described was not a specific streptococcus but one of the alimentary types, causing not a rheumatic carditis, but an ulcerative endocarditis. What is conspicuous by its absence is any alternative proposition as to the bacteriology of this infection.

My own experiences are convincing to myself. On at least three occasions I have seen bacteriologists whose prejudices were against rather than for the streptococcic theory grow a small diplostreptococcus from rheumatic lesions, twice from pericarditic exudate collected after death, once from cerebro-spinal fluid withdrawn from a patient with chorea and carditis who recovered from the illness. Again, histological examination of tissues infected experimentally by animal inoculation with streptococci from human rheumatism shows changes similar in many features to those of human rheumatism. Third, in a form of infection of the human heart by streptococci, subacute bacterial endocarditis, foci of reaction have been encountered, both in the heart itself and elsewhere, which are very closely akin to those of rheumatic infection.

Summary of Part I. There is a type of cardiac inflammation which is well defined histologically as well as clinically. Its characteristics are:

(*a*) It is a pancarditis. All parts of the heart—myocardium, endocardium, and pericardium—are attacked simultaneously and equally.

(*b*) The histological changes are those of intracellular degeneration with interstitial reaction. These latter are focal in distribution, arising in and about blood-vessels and lymphatics.

(*c*) The focal reaction is proliferative, affecting principally the endothelial cells lining small blood- and lymph-vessels and the connective tissues surrounding those vessels.

(*d*) It is like those of other rheumatic tissues and almost certainly runs a brief course as in these others, though recurring from time to time and adding at each outburst to the permanent cicatricial changes seen particularly in the valves and to a less extent in the pericardium.

(*e*) The final stages of post-rheumatic disease of the heart are free from these phenomena, and the patient dies of degenerative changes in the myocardium largely, if not wholly, initiated, sustained, and completed by the mechanical embarrassments which these cicatricial changes impose on the action of the heart.

Reasons are given for regarding this kind of carditis as resulting from invasion of the heart from time to time, through its coronary blood-supply, by streptococci.

Part II.

Progressive Ulceration of the Endocardium.

Introductory. That a majority of cases of ulcerative endocarditis may be traced to streptococcal infection is well known. The following notes are based on an exhaustive examination of hearts from 20 cases of endocardial ulceration in which streptococci were found either during life, or after death, or both. In several other cases examined there are reasons for believing that streptococci were responsible, but as this cannot be proved I am leaving these hearts out of my report. Among the 20 that are included is to be found every degree of intensity of infection. I propose first to indicate those features which seem to me to be common to all these grades.

Features common to all cases. The first point is the overwhelming severity of the endocardial lesions. It is unnecessary to labour the fact that the valves suffer heavily in cases such as these, and that the ulcerative process may also extend widely upon the endocardium lining the left auricle and ventricle, actually burrowing into the muscular substance in some cases. Microscopically, too, the reaction is on a grand scale, infiltrating the whole valve. In 15 out of 20 cases the polymorphonuclear leucocytes played the chief part in this reaction, the exceptions being either very early or very chronic cases. What is not perhaps as generally realized is that the rest of the heart is relatively undamaged. Apart from the old adhesions laid down by pre-existent rheumatic carditis, and an occasionally inflammatory spot in the subpericardial connective tissue, I found no evidence of pericarditis in any of the 20 cases. As for the myocardial lesions, their relative infrequency may best be expressed by reference to three cases illustrating different types of endocardial ulceration. The first is that of a patient with the physical signs of a persistent ductus arteriosus upon which the symptoms and signs of an intense endocardial infection became superimposed. *Post mortem* there was extensive ulceration, not only of the pulmonary valves and the persistent ductus, but also of all the aortic cusps and of the aortic intima. The clot deposited on these surfaces contained masses of streptococci; yet in 48 sections of myocardium examined only 53 inflammatory spots were found, and these were for the most part quite minute. The second case was that of an ex-soldier displaying the clinical and anatomical features characteristic of 'subacute bacterial endocarditis' running a course of many months. The aortic valves were widely ulcerated and in places almost perforated, and the microbic invasion had spread to the endocardium of the left ventricle. In 274 sections of myocardium, a majority of them very large (being serial sections of the cavo-auricular junction and the auriculo-ventricular connections), 13 recent embolic lesions and 20 infarct-scars were noted, no more. The third case was that of a girl with early ulceration of the mitral valves consequent on puerperal infection. In this case, although a number of blocks was examined, only one intramyocardial focus of inflammation could be found, an intense mononuclear leucocytosis radiating

in all directions from a thrombosed arteriole in the interventricular septum. The contrast between this state of affairs and that discovered in rheumatic carditis is very striking. In the latter, though the destruction of endothelial surface is trifling, yet the myocardium is sown with inflammatory foci so freely that it is not uncommon to meet with three or four in one low-power field, while in the hearts of patients dying early in an active phase some sections of myocardium show wide areas of cellular infiltration of an inflammatory type.

The second point common to all cases of streptococcal ulceration of the endocardium is that the myocardial lesions are nearly always obviously vascular in origin. There is much variation in the type and stage of the reaction, a fact to which further allusion will be made below, but this one feature is common to all lesions; they surround a blood-vessel which, in early phases at all events, is itself closed by a clot often containing cocci. Whether this closure is embolic or thrombotic it is difficult to say. In favour of the former view is the fact that vessels narrowed by endarteritis or hypermyotrophy are not more often plugged than those whose lumen is natural in size; also the fact that one not infrequently finds a small mass of cocci filling a vessel but exciting no reaction either in or around the vessel walls, presumably because the embolism occurred just before the patient's death. On the side of the thrombotic view must be set the fact that many small vessels, particularly in the valve and in and about the central fibrous body, display proliferative changes in the intima which sometimes encroach so far upon the lumen as almost to obliterate it. The general impression left on my mind is that in a majority of cases the intramyocardial lesions look as if they were embolic in origin.

And further, as a general rule, it is surprising to find how little reaction is evoked by and around these vascular lesions. This fact will come out in a more detailed form below, when the varying grades of intramyocardial inflammatory inflammation are compared. One kind of myocardial lesion that is certainly not embolic is that which is to be seen at the base of ulcers spreading deeply from the endocardium. In such the adjacent muscle may become implicated in a sort of phlegmonous reaction, and, though this does not as a rule extend deeply, I have notes of a case in which the pars membranacea septi was almost perforated and the left main branch of the *a.-v.* bundle severed. That there is no particular predilection on the part of emboli for lodging themselves in the myocardium is best shown, perhaps, by comparing the relative paucity of such lesions with those to be found in the kidneys. Baehr (15) and Gaskell (16) have taught us that in chronic cases we may expect to find a large number of glomeruli rendered useless by fibrinous plugs received from the cardiac valves, and in several of my cases over half the capillary tufts had undergone this change.

The picture that I have tried to draw, therefore, as outlining the constant features of streptococcal ulceration of the endocardium, is one of a heart in which the valves and mural endocardium are widely and sometimes deeply injured. Such myocardial lesions as are found are relatively trivial in extent, and appear to owe their birth to emboli from the ulcerated endocardium.

Variable features. But though these features—endocardial ulceration and myocardial infarction—are constant, yet they vary widely in detail. The picture which the devastated endocardium displays under the microscope is a compound in varying proportions of two factors: surface necrosis on the one hand opposed by inflammatory reaction on the other. Moreover, the reaction is again compounded in varying proportions of proliferative changes in the fibrous tissue, the surface endothelium, and the blood-vessels of the valve, and exudative changes in which a polymorphonuclear leucocytosis is a predominant feature. Broadly speaking, it is in the intensely toxic cases with much fever and a rapidly fatal course that we meet with extensive necrosis and polymorphonuclear exudation. On the other hand, it is in the type of case that is sometimes labelled 'subacute bacterial endocarditis' that the proliferative element in the reaction attains its highest development. In such the histological picture displayed by the inflamed valve is much like that of the intenser degrees of 'rheumatic' endocarditis, though even in such chronic cases there is apt to be a larger proportion of polymorphonuclear leucocytes and a much wider area of surface necrosis than in the 'rheumatic' lesion. In the chronic type of case, again, the number of cocci visible in the section may be very small. Indeed, in one of my cases, where Dr. Geoffrey Hadfield proved by culture that streptococci of the *S. faecalis* type were present in the surface clots, careful examination of many sections failed to find them. Facts such as these, considered with the absence of inflammatory reaction in the renal changes characteristic of this kind of endocarditis, and with the general constancy in degree of the lesions encountered in such cases, suggest that this group really consists of those cases in which streptococci of a low virulence have just succeeded in getting and keeping a hold on the cardiac valves. In the acute cases the valve may be saturated, not only on its surface but also throughout its depths, with cocci growing in long chains. Such gross infections are naturally met with only in association with grave toxaemia and early death.

When we compare the spots of intramyocardial change with one another we encounter a remarkable range of variations. Sometimes the lesion found is frankly suppurative: a small abscess centring upon a coccal plug in a vessel. In other instances the core of the lesion is a fibrinous plug adhering to the wall of a vessel which is surrounded by a zone of leucocytosis, sometimes principally polymorphonuclear, but in others mainly mononuclear. In others, again, the vascular centre is not apparent, but a group of inflammatory cells in an intermuscular plane is all that is to be seen. These cells may be polymorphonuclear leucocytes solely or chiefly; or cells of lymphocytic type; or—most interesting of all—cells derived from proliferation of lymphatic or capillary endothelia. Such areas as these last are apt to be irregularly stellate in appearance, and are particularly associated with the more chronic type of infection. These will need further notice presently. Another class of myocardial lesion is the irregular radiating scar, sometimes attaining such a size that it can easily be seen with the naked eye, found oftenest in the wall of the left ventricle and the interventricular

septum. Some of these appear so dead that it would be hard to believe them inflammatory if it were not for the presence, at the centre of other such areas, of foci of cellular infiltration of obviously inflammatory nature. And, finally, not seldom one observes a coccal plug obstructing a vessel around which, nevertheless, no inflammatory response has developed, probably because the patient died before it had time to do so.

This wide variability in the kind of reaction to coccal invasion of the myocardium is not due solely to variation in the virulence of the infecting micro-organism, for every kind of intramyocardial focus may be seen in one and the same heart. Neither can it be chiefly explained by the size of the embolus: though this of course has a good deal to do with the size of the area of reaction, for it is inconceivable that some of the big myomalacial areas seen in the more chronic cases are due to anything less than occlusion of a fairly large vessel; but the size of the plug is not everything. Side by side within the same heart may be seen smart reaction round a small clot, with little or no reaction round a big one. The fact is that the length of time that has elapsed since the focus of reaction was first provoked into being has very much to do with its microscopical appearances. Hence the discovery of many cicatricial lesions is a safe index of chronicity, while the predominance of 'petechial' spots—polymorphonuclears huddled together with or without haemorrhagic extravasation—points to a severe and rapidly destructive infection. This, then, is the pathological picture of streptococcal ulceration of the endocardium, whether rapid or slow: a tenacious invasion of the cardiac valves, and (resulting therefrom) embolic lesions of the cardiac wall. This leads us to ask two questions: by what avenue do the infecting organisms gain access to the endocardium? and whence do they come?

Origin of valvular lesions. As to the first question, it is clear that the attack upon the endocardium must be delivered either directly upon the endocardial surface by organisms borne through the heart on the current of the main stream, or through the coronary arteries and the small twigs that pass therefrom into the bases of the cardiac valves. The evidence furnished by histology is conflicting. In favour of the first view may be advanced cases like that of the girl already spoken of, in whom an infection by streptococci was engrafted upon a persistent ductus arteriosus, a condition which presumably invited infection only because it implied a sparing and imperfect development of the phagocytic and defensive intima past which the organisms flowed. And again, a similar argument—defective intima—may be brought forward to account for the comparative ease with which micro-organisms gain a hold on valves already injured by past rheumatic carditis. But, as I have already pointed out, these injured valves are also vascularized valves. The inflammation excited by rheumatic infection was a smart proliferative process, and though it subsided it left the valve full of newly-formed blood-vessels, and thereby provided so many new avenues by which the coronary blood-supply might pour microbes into the substance of the valves.

Again, the fact that in the early stages of some cases of infective endocarditis it is a superficial lesion only that is established seems to point to the adoption of our first hypothesis, namely, that it is on the endothelial surface of the valve that the organisms first secure their hold. Yet there are two data that make one hesitate before receiving this view. First, I have seen sections through the septum membranaceum in which an ulceration of the endocardium on the left side of the heart has been accompanied by proliferation of the right ventricular surface of the septum, without any sign of intervening inflammation. Second, one sometimes sees granulations springing from the surface of the valve and apparently without any subjacent inflammation of the substance of the valve. Nothing could seem a more definite proof of the superficial origin of the inflammatory process. Yet on careful examination of the projecting granulation it may be noted that the endothelium of the valve on either side of it is turned up and continuous with that covering the flanks of the granulation, giving the impression that in its development the granulation has grown up from below and forced the endothelium of the valve in front of it. Again, there are spots which show an apparently superficial reaction, which, however, proves on examination of serial sections to be merely the periphery of an inflammatory focus obviously arising from and particularly concentrated upon a part of the subendocardial connective tissue, and apparently embolic in origin. Finally, the distribution of the inflammatory changes in certain ulcerated valves is such that one can scarcely doubt the deep beginning of some part at all events of the infective process. A long, narrow creek may be found opening to the surface by a small opening, and having for its fundus a ragged suppurative surface. Or one may see several such necrotic areas joining together to 'point' by one common mouth to the endothelial surface, after the fashion of a carbuncle.

It cannot be denied, therefore, that though in some cases the infective process appears to arise, and in others to spread, upon the endocardial surface rather than deep to it, there is evidence that in many cases it arises beneath the endothelium and spreads through to it by a process of lymphatic permeation.

Once the surface has been reached and the endothelium spoilt, fibrin becomes freely deposited, together with organisms from the passing blood-current, and infection and necrosis proceed all the quicker.

Sources of streptococcal infection. The points from which the organisms launch forth on their voyage of attack can only be guessed at in a majority of cases. It is quite certain that they are carried into the heart by the blood-current and not by lymphatic channels. What is not certain is the means by which they gain entrance to the blood-current, at all events in most cases. In two of the patients, whose hearts are under discussion, the infection was obviously puerperal, and the organism was recovered from the uterine cavity. One of these women had already been under my care with the symptoms and signs of mitral stenosis for some time, when to these signs were added all the phenomena of endocardial infection supervening upon a septic puerperium. In the other case there was no clinical evidence of any pre-existing valvular lesion. Another

patient had a very instructive history. I had watched him for years. He came of a remarkably rheumatic family, and by the time he had reached puberty had himself a definite lesion of the heart with aortic incompetence. During the war, for economical reasons, he went through a phase of much hardship and privation. Immediately after this I admitted him to hospital for an influenzal broncho-pneumonia. He recovered slowly from this, and his temperature refused to become normal for weeks. Soon afterwards he was struck down by cerebral embolism, and died from progressive poisoning by a streptococcal infection of his aortic valves. This had, then, been caused by (1) a diminution of general resistance, (2) a pre-existing lesion of the aortic valves, and (3) a streptococcal infection following on influenza with broncho-pneumonia. Many patients, indeed, say that the illness which afterwards proves to be symptomatic of streptococcal ulceration of the endocardium dated from an attack of influenza, but on inquiry one finds almost invariably that the so-called 'influenza' was no more than an attack of fever without obvious cause—no more, in fact, than the initial phase of the endocarditis itself.

The position, then, is this. In a few cases we can easily account for the entrance of streptococci into the circulation. The 'portal of entry' is an obvious one, but in a majority it is not obvious. Yet consideration of several facts will, I believe, lead us to a shrewd guess at the truth. First, there is the fact, attested by many bacteriologists, and particularly in this country by Horder and his colleagues (17), that the streptococci of chronic ulcerative endocarditis are indistinguishable culturally from those of the alimentary canal. Second, we may assume from the analogy of puerperal infection that it is only in a small percentage of those cases in which streptococci are introduced into the circulating blood that the endocardium becomes infected. In agreement with this belief, I have several times seen masses of streptococci in the blood-vessels of a heart which showed no gross or microscopic evidence of recent inflammation. No doubt this infection was agonal, but it may, perhaps, be used as a straw to show which way the wind blows. Third, there is, in a majority of cases, some form of predisposition to infection, either by exhaustion of general vitality, or—what is more definite and tangible—by a pre-existent lesion of the cardiac valves. Putting these points together, it seems probable that many persons become infected with streptococci from the alimentary, and perhaps also from the respiratory, tract, but that this leads to endocardial infection only in a few predisposed persons. As to the means by which the organisms pass through the wall of these tracts, surely the thing to wonder at is, not that they do sometimes pass through, but that they are ever kept at bay, when we consider the enormous area of epithelial surface open to attack, and the ease with which this becomes broken and permeable. And in certain cases there is pretty definite evidence that it is through such breaches of mucous membrane that invasion occurs. In one of my patients, for years the subject of mitral disease, the symptoms of ulcerative endocarditis developed soon after the removal of a number of very septic teeth.

Summary of Part II. 1. Streptococcal ulceration of the endocardium is characterized by:

(*a*) Disproportionately severe lesions of the endocardium.

(*b*) The embolic nature of the myocardial lesions.

The presumption is that (*b*) is secondary to (*a*).

2. The endocardium is invaded sometimes from its surface, sometimes through its own coronary blood-supply.

3. This invasion, predisposed to by local and general defects of resistance, is due in some cases to obvious sources of infection, such as puerperal sepsis. When the source is not obvious, there is reason to suspect invasion of the system by the common streptococci of the alimentary or respiratory tract.

Part III.

The Cardiac Lesions that follow Inoculation of Animals with Streptococci.

Material examined. The material reported on in this section consists of hearts (and other tissues) from animals inoculated with various strains of streptococci. These strains are derived from:

1. Heart's blood of a case of rheumatic endocarditis in a child, collected and cultivated *post mortem* by Dr. Graham Forbes.

2. Pericardial fluid from a case of acute rheumatic carditis with hyperpyrexia, cultivated *post mortem* by Drs. Poynton and Paine.

3. Cerebro-spinal fluid taken during life from a child with chorea who recovered, and cultivated by Dr. G. Scott Williamson.

4. Articular fluid taken *post mortem* from a child with rheumatic carditis and polyarthritis, and cultivated by Dr. G. Scott Williamson.

5. Similar fluid taken and cultivated *post mortem* by Professor J. M. Beattie, from a man dying of acute rheumatism.

6. Blood-cultures taken during life from a case, afterwards fatal, of chorea, polyarthritis, and carditis, by Drs. Lewis and Longcope, of Philadelphia.

7. Blood-cultures taken *post mortem* from a case of chorea, arthritis, and carditis by Professor Wassermann, of Berlin, and inoculated into rabbits by Dr. W. Vernon Shaw.

8. Cultures taken during life from the blood of tonsils of cases of chronic ulcerative endocarditis by Dr. E. C. Rosenow, of New York.

9. Blood taken during life from a child with ulcerative endocarditis, and cultivated by Drs. Miller and Kettle.

10. (*a*) A normal stool, and (*b*) a normal mouth, by Dr. Mervyn Gordon.

A full account of the tissue changes which I found in rabbits inoculated by Dr. E. H. Kettle with strains 1–7 has already been published by Miller, Kettle, and myself (18); and a brief note of those of strain 8 by Rosenow and myself (19).

General account of histology. No obvious cardiac lesions resulted from the inoculations with strain 9, although a very interesting arthritis was provoked;

and such cardiac lesions as resulted from inoculations with strain 10 did not differ essentially from those provoked by the other strains. It remains, therefore, to summarize in a general fashion the leading features of these experimental forms of streptococcal carditis.

First, it is only in some, and not in all, of the rabbits inoculated that lesions are found in the heart. In some cases it was necessary to give very large doses in order to provoke a carditis.

Second, the outstanding feature of the carditis, when it does occur, is the widespread injury done to the endocardium by the ' massive doses ' of cocci which can be seen adhering to the damaged surface. This is not limited to the valves, but spreads freely upon the walls of the cavities. The reaction is a proliferation rather than an exudation, and, though extensive, is not intense when considered in relation to the bulk of the coccal masses.

Third, the myocardial lesions are not easy to find, except in hearts that display gross endocardial ulceration. There was no evidence of pericarditis, except in one rabbit, where the sac had apparently become infected from a focus in the subpericardial tissue.

Fourth, such inflammatory foci as are to be seen in the myocardium are vascular in origin. There may be (*a*) small spots formed wholly of the products of endothelial proliferation, (*b*) larger areas apparently thrombotic or embolic in origin, centring upon an obliterated blood-vessel which may be scarcely recognizable as such, and in which cocci may or may not be visible. Some of these latter lesions were very like the ' submiliary nodule ' of human rheumatic myocarditis in its earlier phases, in that the reaction consists mainly of endothelial and fibroblastic proliferation. The myocardial foci may also consist, however, as often, if not oftener, of (*c*) areas of polymorphonuclear leucocytosis surrounding vessels distended by masses of cocci mingled with fibrin. In general, therefore, the human lesion to which these experimental phenomena are most closely allied is chronic ulcerative endocarditis rather than rheumatic pancarditis.

Summary of Part III. The cardiac lesions provoked by intravenous inoculation of rabbits with various strains of streptococci are found to be similar in their essential features: widespread endocardial inflammation and necrosis, with myocardial lesions of vascular origin. In both tissues endothelial proliferation is often the most striking feature of the inflammatory reaction.

Conclusions.

1. The lesions of the human heart which follow its invasion by streptococci are of two types.

2. The first, occurring during childhood and adolescence, and usually known as ' rheumatic ' carditis, is characterized by the fact that all parts of the heart are simultaneously and almost equally attacked. Nearly always there are many intramyocardial foci of inflammation.

3. The second type of lesion is that known as 'ulcerative endocarditis'. In this the direct attack of the streptococci is delivered upon the endocardium only; such lesions of the cardiac muscle and the rest of the heart as may occur are embolic in origin and secondary to the valvular infection.

4. The changes found in 'rheumatic' pancarditis are very constant in kind and distribution, so much so that it is fair to argue a similar constancy of the conditions predisposing to this form of cardiac infection, as well as of the method of infection.

5. In streptococcal ulceration of the endocardium, on the other hand, every degree of variation is to be seen in the intensity of the morbid changes, both in the valves and in the embolic lesions of the rest of the heart.

6. Among these wide variations in the intensity of the infective processes may be remarked a group of cases of 'subacute' or 'chronic' degree; i. e. of cases in which the infective agent has only just succeeded in maintaining its hold on the heart.

7. There is a sufficiently close similarity in the histology of the myocardial lesions of some of these last cases, those of rheumatic pancarditis and those of experimental 'rheumatic' infection of the heart, to support a belief in a similarity of the infective agent in all cases. The same may be said of a small number of specimens from (*a*) experimental infection of the heart with streptococci from a case of human ulcerative endocarditis, (*b*) experimental infection with streptococci from the normal alimentary canal.

8. Assuming this similarity between the infective agents to exist, the sharp divergence between the two types of human lesion noticed in 1–3 must be due to differences between the circumstances and method of the attack upon the heart.

9. The type of cardiac lesion which results from experimental inoculation (i. e. from introduction of a single large dose of streptococci into the circulation) is more closely akin in its main features to the progressive endocardial ulceration of the human subject than to rheumatic pancarditis.

10. Various considerations, on the other hand, lead to a belief in the causation of human rheumatic carditis by the entrance of small doses of streptococci (of a virulence greater than that of the organisms concerned in the causation of chronic ulcerative endocarditis) over a limited period.

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TWENTY CASES OF ENCEPHALITIS LETHARGICA

WITH PATHOLOGICAL FINDINGS IN FOUR CASES

By W. E. HUME, F. J. NATTRASS, and A. F. B. SHAW

The twenty cases described in this paper have been seen by us in hospital and private practice chiefly within the last year. Though this group does not include all cases of encephalitis lethargica seen by us during that period, an analysis of them brings out the chief signs and symptoms of a disease which has been widespread throughout the British Isles. With the exception of papers published by Edwin Bramwell, and under the auspices of the Local Government Board, few comprehensive accounts of series of cases have appeared in the medical press, though descriptions of isolated cases have been published almost weekly. In our series there were four deaths, and an account of the pathological findings is given in detail. A table is appended which sets forth the essentials of the clinical history and physical signs in each case. This table forms the basis of the clinical summary which now follows.

Age and sex. In this group there were 14 males and 6 females, and the ages ranged from six years to sixty years, the majority being young adults.

Occupation. Of the males the majority were of the artisan class, though case No. 16 was a farmer.

Locality. Twelve of these patients lived in a town, five in a mining district, and three were seen in the country. The districts which supplied these cases were widely separated. Two cases were seen in consultation with the same medical practitioner in the same afternoon, but their residences were at a considerable distance from each other.

Epidemiology. Most of the cases were seen during the autumn and winter, and in only one instance was there any history of personal contact with the disease, a nursing Sister who stated that the last case she nursed in the Army was one of encephalitis lethargica. There was no evidence of catarrhal illness in other members of the household in which the patient was found. Case No. 12 was alleged to have suffered from a similar illness four years previously, during which he was laid up in bed for nine weeks.

The onset of illness was acute in twelve cases and insidious in eight cases.

A. Acute onset. (1) *With fever and delirium.* Five patients were seized with an acute illness with rapid rise of temperature and the early onset of

delirium; for instance, No. 8 was seized with severe occipital headache, quickly followed by delirium. No. 16, a farmer, had been in Newcastle at a meeting, and on arrival home in the evening felt suddenly chilly and complained of headache. He went straight to bed and within three hours was quite delirious, and his doctor recorded a temperature of 103° F. the same night. No. 14 felt intensely giddy on his way to work and came home before starting work. He went to bed and during the morning became actively delirious.

(2) *With fever and neuritic pains.* No. 17 took suddenly ill with shooting pains in the right leg, right arm, and left side of trunk, with rise of temperature. No. 18 commenced with pains in the right leg from the hip to the toes, followed by pains in the left leg. No. 20 was sent to hospital as a case of acute left sciatica with a history that the illness had begun with acute pains in the left side of the head, which spread to the right side of the head, then into the left arm and elbow, and later into the left leg down the left sciatic nerve. These were followed by myoclonic movements of the limbs.

(3) *With acute mental disturbance.* During the first three days of the illness of No. 15 the clinical picture was one of delusional insanity; this was followed by intense lethargy.

(4) *With retention of urine.* No. 4 had suffered from acute diarrhoea for some days, and the first nervous derangement was an acute retention of urine. This patient eventually died.

B. Insidious onset. Drowsiness chiefly characterized the onset in the remaining eight cases. In some, diplopia was either the first or an early symptom, as in the case of No. 11, whose first disability was double vision in a theatre. Occasionally the oncoming drowsiness was very gradual and the patients made efforts to keep awake and attentive to their duties. No. 12 continued at work for five weeks, during which he fell asleep at meal-times, and his work as a draughtsman was made difficult by his recurring diplopia.

Temperature and pulse-rate. It is probable that there was a rise of temperature in all cases at the onset of the illness. Even at a late stage of the illness there was frequently a small evening rise of temperature. The majority of the cases which began acutely had a sharp rise of temperature up to 102° or 103° F. The pulse-rate was usually in proportion to the degree of fever. Hyperpyrexia, immediately before death, up to 104°·5, 105°, and 106° F. occurred in three of the four fatal cases.

Lethargy. Of the twelve cases with an acute onset eight became definitely lethargic and drowsy. In three the drowsiness was very marked and prolonged, while in the case of No. 16 there was marked drowsiness for three days, with rapid and complete recovery from an illness which only lasted altogether about seven days. Of the eight cases with an insidious onset abnormal drowsiness was the first feature of the disease in three cases, and drowsiness and diplopia were the earliest manifestations in two cases. In some of the cases with an insidious onset drowsiness became daily more marked, until at the end of four or five weeks definite lethargy developed and the patients remained constantly asleep. The

lethargy is the most striking feature of the disease: the smoothed-out features with paresis of the facial muscles give the patient a peculiarly stolid appearance and intensify the inanimation. Some of our patients, for variable lengths of time, slept the whole of the 24 hours and had to be roused for every nursing attention and for feeding. When roused it was impossible to get the patient to fix his attention on anything for any length of time; he seemed to be mentally exhausted, and in a moment appeared to drop off to sleep again. Those patients who had been markedly delirious subsequently developed lethargy.

Nervous System.

(1) *Diplopia.* Twelve patients complained that they 'saw double' during some period of the illness. In six there was definite paralysis of ocular muscles. The external rectus was the muscle most frequently affected, and it was paralysed on the right or left side in five cases. In some cases (five) the patient complained of double vision, but, on testing, it was difficult to decide which muscle or muscles were at fault. The ocular paralysis was frequently evanescent, and this fact is in keeping with the description of focal oedema without cellular exudate in the pathological report.

(2) *The pupils.* In most of our early cases it was noticed that the pupils were dilated and did not react to light or accommodation, but this early observation did not turn out to be so constant in the later cases. In three cases the pupils were completely inactive to light and accommodation, and a poor and sluggish reaction was obtained in five cases. In five cases the pupils were considerably unequal, though they reacted to light and accommodation.

(3) *Ptosis.* In two cases there was very obvious bilateral ptosis.

(4) *Nystagmus.* Nystagmus was present in two cases.

(5) *Optic neuritis.* The disks were frequently examined in all cases and there was never any evidence of choked disk or neuritis.

Though only recorded in the notes of one case, many of our patients made complaint of what they called 'haziness of vision' (paresis of muscles of accommodation).

(6) *Trismus.* Trismus was a marked feature in two cases.

(7) *Seventh nerve.* Paresis of one side of the face was noted in five cases and was inconstant in some, similar to the inconstant paralysis of the ocular muscles. This paresis is to be distinguished from the restricted movement of the facial musculature which characterizes the 'Parkinsonian mask'. In the five cases in which there was a marked difference in power of the muscles of the two sides of the face it was assumed that there was a nuclear lesion on the affected side. In the majority of the cases there was a general 'smoothing out' of the face, giving rise to a stolidity or lack of expression which was, in many, a very marked feature. This 'smoothed-out' appearance or 'Parkinsonian mask' is probably dependent upon changes in the basal ganglia.

(8) *Hypoglossal nerve.* The right side of the tongue became definitely paralysed in one case in this series (No. 8), though we have seen the same paralysis in another case not included in this series.

(9) *Speech.* Speech was, in some cases, slow and monotonous and resembled that of paralysis agitans.

(10) *Involuntary movements.* (*a*) *Fine tremors.* Fine tremors of various groups of muscles characterized four cases. In two cases these tremors were associated with monotonous speech and marked smoothing of the face, and the clinical picture bore a general resemblance to paralysis agitans.

(*b*) *Myoclonus.* Myoclonus of various groups of muscles was very noticeable in fourteen cases. In nine the limbs were chiefly involved. The abdominal and back muscles were involved in three cases and the face and jaw muscles in two. The abdominal and back muscles were particularly affected in No. 18. Sometimes the myoclonus sufficiently affected the muscles to produce gross movements of the limbs so that there were jerky involuntary movements, and at other times groups of muscle-fibres were seen to contract without any corresponding movement of the limb.

(*c*) *Rigidity.* Marked katatonia was observed in No. 15. In some, rigidity of the neck suggested meningitis, and this was particularly marked in No. 4, and, to a less extent, in Nos. 1, 3, and 10.

(11) *Reflexes.* (*a*) *Knee-jerks.* In most cases the knee-jerks appeared normal, but in six there was some departure from the normal. In No. 3 no knee-jerks could be obtained, in No. 18 they were sluggish, and in three cases there was considerable disparity on the two sides. In No. 7 knee-jerks were much exaggerated and associated with patellar and ankle clonus.

(*b*) *Plantar response.* In six cases, at some period of the illness, there was a definite Babinski's sign on one or both sides. In three cases a double Babinski was obtained and in three on one side only.

(12) *Sphincters.* The nervous symptoms in one case (No. 4) first appeared as complete retention necessitating catheterization. One other case had occasional retention of urine (No. 18). Three other cases had temporary incontinence of urine.

Cerebro-spinal fluid. This was examined in eight cases. In all, the fluid was under pressure and clear. There was a small coagulum in one case (No. 4) and no coagulum in seven cases. A lymphocytosis was obvious in four cases: these were well-advanced cases and the lymphocytosis tended to appear late in the disease. An excess of reducing substance is recorded in two cases and an excess of globulin in two. In all cases there was an absence of growth on ordinary culture media. In our early cases, five in number, Wassermann reactions were done on the cerebro-spinal fluid and invariably proved negative.

Course of the disease. There were four deaths on the 15th, 20th, 22nd, and 30th days from the onset of symptoms.

One case, No. 16, had an extremely acute illness with complete recovery within one week from the onset. One case, No. 9, recovered completely in six

weeks. Six cases recovered completely in periods varying from eight to twelve weeks. Seven cases were recovering slowly some months after the onset. All of these cases were sufficiently well to be up and about for the greater part of the day, but retained a tendency to drowsiness and were slow in their movements. The type resembling paralysis agitans was the slowest to recover, and some degree of the facial mask was one of the most persistent features. One case, No. 15, started with delusions which commenced with delusional insanity, and remains still melancholic, but his delusions have ceased and there is no further sign of insanity.

Diagnosis.

A diagnosis of encephalitis lethargica should always and only be made by a process of exclusion of other possible diseases. A combination of two or more of the following signs and symptoms would always suggest the possibility of this disease:

1. Fever at the onset of an illness.
2. Acute mental disturbance.
3. A gradually increasing lethargy.
4. A clinical picture of paralysis agitans, with a smoothed-out facial appearance, general rigidity of the musculature, together with tremors.
5. Myoclonus.
6. Neuritic pains distributed down the limbs and alternating from side to side.
7. Ocular paralyses, which include squinting, inability to range the eyes upwards, inaction of the pupils particularly in response to light.

In our cases the patient frequently complained of a general blurring of vision. When the disease is suspected from the appearance of any of the above phenomena particular attention must be paid to the optic disks and to the cerebro-spinal fluid. In no case of encephalitis lethargica have we been able to detect any evidence of a choked disk or optic neuritis. In our experience the presence of optic neuritis militates strongly against the diagnosis of encephalitis lethargica. The findings in the cerebro-spinal fluid are usually negative, though occasionally the fluid is under pressure and there may be a slight lymphocytosis with increase of the globulin content. In cases with symptoms of meningitis a Wassermann reaction ought to be done, both on cerebro-spinal fluid and on the blood.

The two following cases exemplify the difficulties in arriving at a proper diagnosis in cases simulating encephalitis lethargica.

One case is that of a boy aged 10 years, who presented a picture resembling so closely encephalitis lethargica that we originally intended to include him in this series. His illness is stated to have commenced suddenly three weeks before admission to hospital with delirium and twitching of muscles. On admission he was markedly drowsy, but could be roused to answer questions intelligently. At times the lethargy was interrupted by periods of active delirium. No fever was observed. There was complete paralysis of the left third nerve and ptosis gradually developed on the right side. In addition, there was weakness of the

left side of the face. The knee-jerks were normal and the plantar responses flexor for the most part, but, at times, a left Babinski response was obtained. The boy lay in an attitude simulating decerebrate rigidity with extension and pronation of the forearms and extension of the lower limbs. At times this attitude was accentuated by tonic spasms without loss of consciousness. There was some degree of katatonia of the upper limbs. The optic disks were normal, and the cerebro-spinal fluid was under pressure, showed a slight lymphocytosis, and contained no organisms. This condition persisted for several weeks unchanged, and then he developed double optic neuritis. At the autopsy a tuberculous tumour was found occupying nearly the whole of the mid-brain and the upper part of the pons, with smaller deposits in the cerebral cortex. Occurring at a time when encephalitis lethargica was epidemic, this case was very deceptive until the onset of optic neuritis.

The second case was that of a woman aged 27 years, who was admitted to hospital with the complaint of drowsiness of several weeks' duration. This had arisen insidiously, and she had fallen asleep when about her daily work. On admission the drowsiness was only slight, and no abnormality was found on examination of the nervous system. She was, therefore, discharged ten days after admission. Three months later she was readmitted with the history that she had been quite well for six weeks after discharge, and then drowsiness had recurred and had gradually become intense. The optic disks were normal, and no abnormality was found in the remaining cranial nerves, the only abnormal nervous sign being a double extensor plantar response. The patient died within a week of her second admission, and at the post-mortem a round cyst about one inch in diameter was found occupying and distending the cavity of the third ventricle: the exact origin of the cyst has not yet been determined.

Treatment.

No specific treatment has been discovered for this disease. The various remedies employed by us in our series do not appear to have influenced the course of the disease.

1. *Urotropin.* Urotropin was administered intravenously and by the mouth in some of our earlier cases. This method of treatment was, apparently, innocuous; it certainly did not alleviate in any way.

2. *Repeated lumbar puncture.* In two cases lumbar punctures were repeated three and four times. In one case immediately after the first puncture a definite left facial paralysis disappeared. We have often noted that such paralyses are fleeting, and possibly on this occasion it was a mere coincidence. In no case was an attempt made to produce a fixation abscess, a method of treatment strongly advised by the French, and we are, therefore, unable to express an opinion on it.

We acknowledge the help we have received from Dr. Davidson, Medical Registrar at the Royal Victoria Infirmary, in compiling the tables.

Description of Cases.

Case 1. M., aged 30. **History of onset:** Onset with numbness down arms, but continued at work as miner for 9 days, when he was overcome by drowsiness. **Condition when first seen:** *14th day.* Muttering delirium. Very drowsy and sweating profusely. Myoclonus of face, jaw, and shoulder muscles. Slight head retraction and Kernig's sign. **Temperature and pulse:** 102° F., rose to 106° before death. Pulse-rate 150. **Mental state:** Semi-conscious. Muttering delirium. **Lethargy:** Marked. **Sleep:** Rapidly became unconscious. In hospital one day. **Cranial nerves:** Paresis of left external rectus. Sluggish and incomplete reaction of pupils to light and accommodation. **Involuntary movements;** Myoclonus of facial, jaw, shoulder, sternal, and abdominal muscles. **Limb reflexes:** Knee-jerks exaggerated. Ankle clonus present. Doubtful extensor response—left foot. **C.S. fluid:** Clear and under pressure. No coagulum. No T.B. and no growth. Dextrose ++. Globulin +. **Course of the disease:** Death on 15th day. P.M.

Case 2. F., aged 27. **History of onset:** Gradual onset of heaviness and drowsiness, but went about the house until drowsiness forced her to stay in bed. Some fever. Some delirium. Fixity of pupils. **Condition when first seen:** *12th day.* Semi-comatose, but could be momentarily roused. Expressionless. Tremors of groups of muscles. Temporary glycosuria and acetonuria. Six months pregnant. Wassermann negative. **Temperature and pulse:** 101° to 103° F. Rise to 105° before death. Pulse-rate 130–140. **Mental state:** Semi-conscious. **Lethargy:** Marked. **Sleep:** Sleepless at onset, then lethargy and unconsciousness. **Cranial nerves:** Pupils did not react to light or accommodation. No squinting observed. Marked paresis of both sides of face. **Involuntary movements:** Early tremors of various muscles. **Limb reflexes:** Double extensor response. Knee-jerks obtained. **Sphincters:** Incontinent. **C.S. fluid:** Not examined. **Course of the disease:** Death on 20th day. P.M.

Case 3. M., aged 30. **History of onset:** Onset with pains in the head and fatigue. Felt sleepy, but unable to obtain sleep. Stayed about the house for one week, then sent to bed by doctor—became delirious. **Condition when first seen:** *20th day.* Had been delirious for six days, wandering and picking at bed-clothes—could be roused. 'Smoothed-out' appearance. Slight double ptosis. Pupils sluggish. Slight rigidity of neck. Wassermann negative. **Temperature and pulse:** 99° to 101·5° F. Pulse-rate 84–108. **Mental state:** Semi-conscious. Muttering delirium. **Lethargy:** Marked throughout. **Sleep:** Sleepless at first, before onset of delirium. **Cranial nerves:** Ptosis. Paresis of left face. Sluggish reaction of pupils to light. Inability to converge on accommodation. Horizontal nystagmus, especially to left. **Involuntary movements:** Twitching of left shoulder and arms in early stages. **Limb reflexes:** Knee-jerks not obtained. Plantar responses flexor. **C.S. fluid:** Clear and under pressure. No coagulum. No T.B. and no growth. **Course of the disease:** Death on 30th day. Intravenous injections of urotropin. P.M.

Case 4. M., aged 6. **History of onset:** Heaviness and dullness. Acute diarrhoea which disappeared after 5–6 days, followed by retention of urine. General condition suggested tubercular meningitis to his doctor. **Condition when first seen:** *17th day.* Temperature 99° F. Pulse-rate 116. Generally quiet with outbursts of crying. Stiffness of neck. Myoclonus of both arms and legs. Retention of urine. Sordes mouth. **Temperature and pulse:** 99° to 102° F., rose to 104·5° before death. Pulse-rate 116–152. **Mental state:** Semi-conscious. **Lethargy:** Marked. **Sleep:** Semi- to unconscious. **Cranial nerves:** Complete paralysis of right external rectus. Pupils dilated and react poorly to light. **Involuntary movements:** Myoclonic movements of arms and (less marked) of legs. **Limb reflexes:** Knee-jerks very active. Babinski's response both sides (temporary). **Sphincters:** Retention of urine. Bowels opened by enema alone. **C.S. fluid:** Clear and under pressure. Small coagulum. Lymphocytes +. No T.B. and no growth. **Course of the disease:** Head retraction became very marked. Death on 22nd day. P.M.

THE MORBID ANATOMY.

(From the Pathological Departments of the Royal Victoria Infirmary and College of Medicine, Newcastle-upon-Tyne.)

Case No. 1. (Record 256/20.)

Autopsy. No gross changes apparent in the thoracic or abdominal organs. The cerebral pia-arachnoid is congested and oedematous; there is no evidence of meningitis, haemorrhage, or thrombosis. The brain is heavy and, on section, oedematous. In both the grey and white matter of the cerebrum and cerebellum there is hyperaemia, which is even more marked in the basal ganglia, mid-brain, and pons. No haemorrhages or softening are seen. The ventricles contain clear fluid and are not dilated.

There are no gross changes in the brain which can be regarded as peculiar to the disease, and this also applies to the appearances found in other cases here recorded.

Histology.

Cortex. (Precentral convolution.) In the pia-arachnoid the vessels are congested, and around a few veins there is slight infiltration with various types of round cells.

In the brain substance there is perivascular infiltration confined to a few precapillary veins in the subcortical white matter, where some scattered round cells are lying in the meshes of the adventitia. The endothelial cells of the capillaries are swollen and project into the lumen, and, though there is no evidence of proliferation of the capillary walls, many of these vessels are outlined by single chains of plasma-like cells lying along the exterior.

A diffuse cellular infiltration of moderate degree affects both grey and white matter. Though a few lymphocytes are present, plasma cells are the chief elements, and no polymorph leucocytes are observed. Around many of the nerve-cells, four up to ten cells are seen, and these lie close to or may project into recesses in the neuron, but there is no definite evidence of neuronophagy.

Basal ganglia. Here the vascular and inflammatory changes resemble both in nature and degree those seen in the cortex. Perivascular infiltration is, however, more marked, though comparatively few vessels are affected and parenchymatous infiltration is more accurately limited to the grey matter.

Pons. In the membranes over the base the changes are similar to those in the cortical meninges, though congestion is more marked and small perivascular haemorrhages composed of well-preserved red cells are present. In the main, the changes in the pons resemble those in the cortex and basal ganglia, but they are more pronounced.

On the whole the changes found in this case are comparatively slight.

Case No. 2. (Record 265/20.)

Autopsy. There are petechial haemorrhages in the pleura and pericardium. Apart from terminal congestion the lungs show no special change. The heart-muscle, liver, kidneys, and suprarenals show evidence of acute toxic change, while the spleen is slightly swollen and the lymphoid tissue is prominent.

There is oedema of the pia-arachnoid, which shows opacities from chronic thickening, but there is no evidence of meningitis. The brain is heavy and moist from oedema, while both the grey and white matter of cerebrum and cerebellum are distinctly congested. In the basal ganglia, mid-brain, and upper half of pons the hyperaemia is considerable. The ventricular system is not dilated and contains clear fluid. There are no haemorrhages or areas of softening.

The uterus contains a six-months foetus.

Histology.

Cortex (including precentral convolution). There is slight chronic thickening in the pia-arachnoid, while the vessels are engorged and the meshes are oedematous. Scattered round cells are present, but no perivascular infiltrations, haemorrhages, or thromboses are found.

There is a marked degree of vascular engorgement affecting all types of vessels. In a few medium and precapillary veins situated at the junction of the grey and white matter the meshes of the adventitia contain a few cellular elements, among which are some large mononuclear cells phagocytic for red cells or pigment. Haemorrhages are not observed.

Basal ganglia. (Corpus striatum and putamen.) Here the vascular changes are more striking than in any of the other situations already described. Both in the grey and white matter many medium and precapillary veins are enveloped in cellular mantles of variable thickness, but the arteries are rarely involved. As a rule the vessel is greatly distended with blood and the endothelial cells are swollen and project into the lumen. In the adventitia of the vessel the connective tissue cells often appear to be increased in number, and occasionally they show evidence of division. Their nuclei are swollen, pale, and vesicular.

Pons. Here the lesions resemble those seen in the basal ganglia. At the same time neither perivascular infiltration nor parenchymatous changes are so marked. Fibrinous thrombi occur in a few vessels, but there are no haemorrhages.

Case No. 3. (Record 349/20.)

Autopsy. In the lower lobe of each lung there is an acute broncho-pneumonia of haemorrhagic type. Petechial haemorrhages are seen in the pleura and peri-

cardium. The heart-muscle, liver, and kidneys show evidence of acute toxic change. Spleen is slightly enlarged but firm, and the lymphoid tissue is not unduly prominent. There is nothing of note in the gastro-intestinal tract. The pia-arachnoid is distinctly congested and rather oedematous, but there are no haemorrhages or thromboses and no evidence of meningitis.

The brain is heavy, soft, and oedematous. In the cerebrum there is considerable hyperaemia—more marked in the white matter. In the basal ganglia, mid-brain, and upper pons the hyperaemia reaches a maximum. The cerebellum is slightly congested. Nowhere are gross haemorrhages present. The lateral ventricles are slightly dilated and contain blood-stained fluid.

Histology.

Cortex. (Occipital lobe.) The membranes are congested and oedematous, though there is no evidence of cellular exudate or haemorrhage. Throughout the cortex there is pronounced hyperaemia which renders the capillaries conspicuous, while many of them are outlined by a row of plasma-like cells. There is often oedema of the brain-tissue in the immediate vicinity of these vessels. In the subcortical white matter a few precapillary veins show scattered cells in the adventitia, but apart from these the vessels are unaffected. Around one venule in the white matter there is a small haemorrhage of red cells in a good state of preservation, which compress but do not lacerate the surrounding tissue. No thrombi are observed. There is a moderate diffuse infiltration of the parenchyma with inflammatory cells of the usual type, and this is more evident in the deeper layers of the grey matter and the vicinity of vessels in the white matter.

Optic thalamus. (The sections include ependyma of ventricle.) Here the hyperaemia is more marked than in the cortex, and especially immediately beneath the ependyma, where there are several small haemorrhages. These have occurred in connexion with both venules and capillaries in which there is no perivascular infiltration, and exhibit different degrees of extravasation.

Mesencephalon and pons. (Sections from lower end of mid-brain and upper end of pons, including 3rd and 4th cranial nerves and motor root of 5th nerve.) The meninges are oedematous and there are small haemorrhages and traces of perivascular infiltration. In both mid-brain and pons the changes greatly exceed those seen elsewhere. The majority of the medium and precapillary veins in the grey matter around the Sylvian aqueduct, the floor of the 4th ventricle, and the raphé, and in the cranial nuclei are enveloped with cellular mantles of variable size in which the cells are of the usual type. In the more ventral parts isolated veins show similar changes, and a few haemorrhages with laceration of the brain are found in the substantia nigra, though in this part the inflammatory changes are inconspicuous. Fibrinous thrombi are seen here and there. There is considerable parenchymatous infiltration, which generally corresponds in distribution to the vascular changes, spreading out in a wide and irregular manner from the affected vessels.

Cerebellum. Here there is no special abnormality. There is considerable hyperaemia, which, however, is not accompanied by inflammatory change, and the Purkinje cells appear to be intact.

Case No. 4. (Record 365/20.)

Autopsy. Apart from acute bronchitis the lungs show no special change. There are a few petechial haemorrhages beneath the endocardium. The heart-muscle, liver, and kidneys show acute toxic change. The spleen is not enlarged and shows no special abnormality. Suprarenals—no gross change. In the stomach, small intestine, and colon there is evidence of acute catarrh and slight swelling of the lymphoid tissue; there is no ulceration. The mesenteric and colonic glands are rather swollen and injected, but show no evidence of tubercle. The vessels over the surface of the brain are engorged and there is oedema in the pia-arachnoid, but no evidence of meningitis. In the basal cisterns the fluid is blood-stained. The brain is heavy and oedematous. There is decided hyperaemia in both the grey and white matter of the cerebrum, but this is not apparent in the cerebellum. In the basal ganglia and pons the congestion is more marked, while minute haemorrhages are seen in the upper part of the latter. There are no gross haemorrhages, thromboses, or areas of softening. The ventricles contain blood-stained fluid, but are not dilated.

Histology.

Cortex. (Frontal lobe.) There is hyperaemia and oedema in the membranes with slight perivascular infiltration in which polymorph leucocytes are rather numerous. A vein with a fibrinous thrombus and a few haemorrhages are the only other changes of note.

In the subcortical white matter and the deeper layers of the grey matter there are several veins with fibrinous thrombi and slight perivascular infiltration in which polymorph leucocytes are evident. These cells, however, are not seen along with the plasma-like cells which outline many of the capillaries. There are no haemorrhages. While diffuse oedema is seen there are several instances where a venule is the centre of an irregular zone of intense focal oedema. Here the nerve-fibres are widely separated and the nerve-cells are compressed, while a few inflammatory cells and binucleated glia-cells lie in the spaces along with nuclear fragments.

Basal ganglia. (Lenticular nucleus.) Here there are changes of great intensity. In several places the veins in the grey matter show considerable perivascular infiltration and frequently fibrinous thrombi.

Pons. (Including floor of 4th ventricle and nucleus of 6th nerve.) In the membranes on the ventral surface a few veins emerging from the brain show a definite collar of perivascular infiltration. Apart from oedema the meninges show no special change. The pontine lesions, while they resemble those in the basal ganglia, are even more pronounced, both in extent and degree.

Cerebellum. (Cortex.) Apart from hyperaemia no inflammatory changes are observed and the Purkinje cells appear to be normal.

Summary.

In the series of cases here recorded the changes correspond, in the main, to those which are recognized as constituting the histological picture of encephalitis lethargica. There are, however, a few points which appear to be deserving of mention.

In the first place, no organisms were found, histologically, save in one case in which diplococci were observed in the basal ganglia, but the distribution of these organisms left little doubt that they were contaminations.

In Case 1 it is probable that the short duration of the illness—15 days—explains the slight degree of inflammatory reaction and the absence of neuronophagy.

In Case 4—a child of 6 years—the intensity of the focal oedemas and, more particularly, the abundance of polymorph leucocytes which, in places, almost presented the appearance of miliary abscesses, are distinctly unusual features. To judge by the length of the illness—22 days—there is no reason to suppose that the presence of so many polymorph leucocytes indicates a virulent type of infection, and it may be that the age was a possible factor in determining the type of exudate. At the same time the lesions, in this case, bear a striking resemblance to those produced in some cases of experimental encephalitis in animals.

Glia-cell proliferation has occurred in all the cases, but multinucleated forms of these cells were never observed. It is suggested that where such formations have been described they are really pseudo-giant cells produced in the process of neuronophagy by accumulation of phagocytes within the residue of a nerve-cell. Although neuronophagy has been present in three of the cases and in all parts examined except the cortex, yet it has never been comparable either in frequency or in character with that seen in poliomyelitis. Invariably the phagocytes have been mononuclear cells, even in Case 4, where polymorph leucocytes were numerous; and the glia-cells—though they have shown evidence of proliferation—do not appear to take an active part in phagocytosis. The lipochrome pigment—normally present in nerve-cells—seems to vary considerably in amount. In the early stages of neuronic degeneration it may be increased, while in the course of neuronophagy it is engulfed by phagocytes which carry much of it away to the adventitial meshes of the veins. The amount of this pigment, both in phagocytic cells and lying free in the tissues, appears to constitute a rough index to the amount of neuronophagy which has taken place. Focal oedema has been frequent—especially in the brain-stem and basal ganglia. While it was usually associated with infiltration of inflammatory cells there was distinct evidence that it occurred independently, and this was observed both in cranial nuclei and other

areas of grey matter. Sometimes the oedema was sufficient to produce definite compression of nerve-cells and stretching of the nerve-fibres, though the cells themselves showed no evidence of degeneration.

On the whole the histological picture has been characterized by the vascular and inflammatory reactions, while degeneration and destruction of the nerve-cells have not been proportional to these changes.

In all the cases, structures apparently identical with those described by Da Fano as ' minute bodies ' have been observed. Though evident enough in another series, not included here, in the present group they were scanty and difficult to find. They were confined to degenerated neurons in the basal ganglia and brain-stem, and were not detected elsewhere.

ON DROPPING OF THE STOMACH: A STUDY BASED ON A SERIES OF 150 CASES

By PHILIP CRAWFORD CONRAN

(From Duff House, Banff)

With Plates 1–5

Introduction.

Since Morgagni first drew attention to the subject in his treatise *De Sedibus et Causis Morborum*, an increasing number of authors has dealt with the various displacements to which the abdominal viscera are liable. Perhaps the stomach has received more attention from them than any other viscus, probably owing to the greater facility with which its position could be ascertained even before the advent of the Röntgen rays. It is only, however, since the introduction, in 1899, of the radiographic method of examination after an opaque meal that accurate observation has been possible ; and not until the past decade has the value of such an examination become widely recognized.

On perusing the literature of gastroptosis, the reader, at an early stage of his inquiry, is impressed by the lack of agreement as to what degree of dropping of the stomach is to be regarded as abnormal.

It is obvious that until the position of the stomach, as shown by X-ray examination after an opaque meal of constant weight and consistence, has been observed in a long series of apparently healthy persons, it will be impossible to state with certainty that an organ, the great curvature of which reaches a point 2½ cm., 5 cm., or even farther below the iliac crest, exhibits an aberration from the normal. For example, Baetjer (1) found that in a series of selected individuals, all athletes, all thin, but in condition and having no symptoms, each showed more or less visceroptosis.

Uncertain as the normal position of the stomach may be, we can, nevertheless, broadly assume that, in a series of cases collected for the purpose of analysis, the lower the level reached by the gastric shadow the more probable is it that we are dealing with a pathological condition.

I have selected for the present purpose only the more severe cases, namely, those in which the gastric shadow reached a point approximately 10 cm. below a line joining the summits of the iliac crests, my study being ultimately based upon

a consecutive series of 684 patients who, on admission to Duff House, complained of one or more symptoms suggesting some derangement of the alimentary canal, and who were consequently all subjected to a routine X-ray examination.

A large proportion of these patients were in my immediate charge throughout, under the supervision of Dr. E. I. Spriggs. The radiographic examinations were carried out by Mr. O. A. Marxer, and the analyses of the gastric contents by Mr. A. J. Leigh, B.Sc., F.I.C.

Method employed in Radiological Examination.

All the cases mentioned were radiologically examined by Mr. O. A. Marxer in accordance with the following procedure:

One fluid ounce of castor oil is taken at 10 p.m. in order to clear the canal. Twelve hours later, before breakfast, film and screen observations are made of the heart, chest, and solid abdominal viscera, and of the biliary and renal tracts.

Thirty-six hours after the castor oil has been given—that is, on the morning of the second day—instead of the usual breakfast an opaque meal is taken, which is prepared by mixing 150 grm. of barium sulphate with sufficient butter-milk to bring the volume up to 500 c.c., and is flavoured with cocoa. While drinking this the patient stands facing the observer, on a platform, with the anterior abdominal wall touching a fluorescent screen as in Fig. 2. At a fixed distance of 75 cm. behind the screen is the tube, and between them is a rectangular adjustable diaphragm, also at a fixed point. The tube is centred by means of a second tubular diaphragm of a small and fixed diameter. When the tube is accurately centred a circular patch of light is thrown on the screen of approximately the same area as that of the diaphragm aperture, the rays being almost parallel.

If an opaque object, of a diameter smaller than that of the beam, is now interposed, the measurements of the shadow will correspond almost exactly with the surface measurements of the object.

If a larger object is employed, and the rectangular diaphragm aperture is enlarged sufficiently, it will still be possible to obtain a complete shadow on the screen; but the rays will be more and more divergent towards the periphery of the beam, and the shadow will be larger than the object. The nearer, however, the object is to the screen, the less will be the distortion of the shadow.

On applying these facts to the present case it is evident that when the patient stands with the abdomen touching the screen, there will be a certain degree of exaggeration in the apparent length of the stomach, as estimated by its shadow. Almost invariably the stomach is tilted backward, so that, when the tube and diaphragm are on a level with its mid-point, the shadow extends farther upwards than the true level of the highest point of the cardia, whereas the bottom of the shadow corresponds more closely with the lowest part of the organ (see Fig. 3).

The extent of error due to this divergence of the X-rays varies directly with the length of the stomach, as is shown by Figs. 2 and 3, and due allowance must

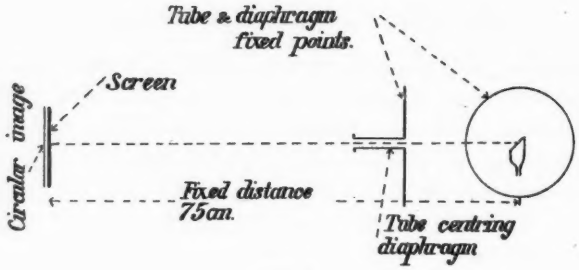

FIG. 1.

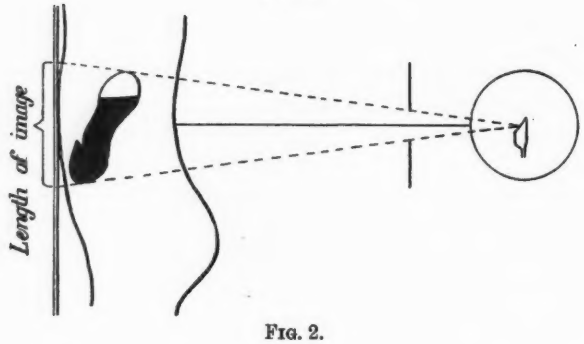

FIG. 2.

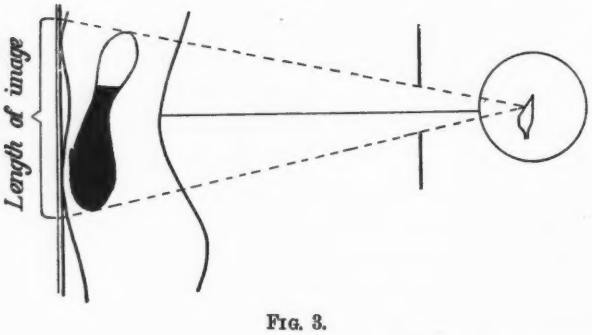

FIG. 3.

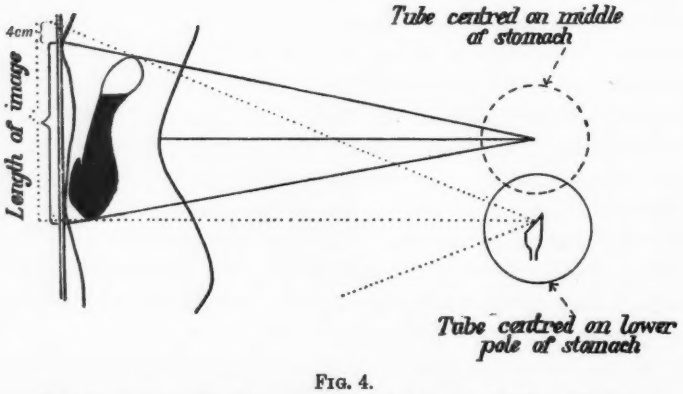

FIG. 4.
Variations in length of image with central beam at different levels.

be made for it, although in practice it is found to be very small in the case of the lower pole.

Like the upper pole of the stomach, the highest points of the iliac crests lie at a considerable distance from the screen, so that their position can only be gauged with difficulty. For this reason Mr. Marxer now takes the centre of a line joining the anterior superior spines, which lie close to the screen, and the upper end of the symphysis pubis as the fixed points from which measurements are made.

Midway between these two levels the shadows of the lower ends of the sacro-iliac synchondroses are seen.

On viewing the shadows of a large number of stomachs, with the tube and diaphragm first on a level with the mid-point of the shadow, and then on a level with the lower pole, it has been found that, on an average, when in the first position the bottom of the stomach shadow is on a level with the shadow of the lower end of the sacro-iliac synchondrosis, observation in the second position shows that the stomach actually reaches a point 10½ cm. below a line joining the highest points of the crests of the ilia (Fig. 4).

This fact has proved of considerable practical use in estimating the extent to which a stomach is dropped, and, in the illustrations later on, it will be seen that in all the 150 cases the lower border of the shadow approximates to, or exceeds, this limit. A further point worth noting is that while observing the stomach with the tube and diaphragm on a level with the lower pole there may be an error of 3 or 4 cm. in the apparent length of the stomach, as compared with its length when viewed with the tube centred on the mid-point of the shadow (Fig. 4).

Having also observed the shape, size, position, and tone of the stomach, the nature of the peristalsis, and the regularity or irregularity of its outline when viewed from various angles, one or more plates or films are obtained as follows:

First, in centring the beam, the rectangular diaphragm aperture is enlarged sufficiently to show both lower and upper parts of the stomach, the latter on expiration. The aperture is then enlarged still more, so that both the stomach and its bony surroundings are included in the area of a plate, which is then placed in position and exposed.

The patient is then examined when in a horizontal position, both prone and supine. The duodenum is observed and films are exposed, and, thereafter, screen and film observations are made 1, 4, 8, 24, 36, and 48 or more hours after the taking of the opaque meal until the bowel is empty of barium, the intervals varying according to the findings, and the patient remaining throughout within call of the X-ray room.

Finally, if an abnormality of the lower bowel is indicated, or if it has not been seen well filled, a barium enema is given and the result noted. The advantages of barium sulphate as an opaque medium are (1) that it is lighter and cheaper than the bismuth salt; (2) that it is insoluble in water and acids, and passes through the whole canal without undergoing any chemical change (it is completely inert even in those cases of diarrhoea which are arrested

by bismuth salts); (3) that, as a series of observations has shown us, both the duodenum and appendix are better seen than if bismuth is employed.

Groedel and Maase (7), by giving experimental feeds of powdered bone and of bismuth alternately, claim to have shown that the presence of bismuth in the stomach has no effect in producing distortion of the organ, the X-ray appearances being exactly similar whichever of these substances was used. The same would, *a fortiori*, be true of the lighter barium salt.

Complications.

In 50 of the 150 cases of gastroptosis some other lesion was found to which some of the symptoms or signs mentioned later might reasonably be attributed. With a view to ascertaining whether these lesions tend to be especially associated with a dropped stomach a comparison was made with an equal number of patients, that is, 150, who complained of digestive symptoms, but in whom the stomach was found to be in a comparatively normal position.

The following table shows the result:

TABLE I. *Lesions complicating Gastroptosis Cases and those with Stomach in Normal Position respectively.*

Lesion.	Number of Gastroptosis Cases showing it.	Number of Other Cases showing it.
Appendicitis	16 (11 %)	30 (20 %)
Duodenal ulcer	9 (6 %)	7 (5 %)
Arthritis	8 (5 %)	4 (3 %)
Pulmonary tuberculosis	7 (4 %)	4 (3 %)
Colitis	6 (4 %)	8 (5 %)
Gastric ulcer	3 (2 %)	9 (6 %)
Renal calculus	2 (1 %)	2 (1 %)
Sprue	2 (1 %)	1 (1 %)
Diabetes	2 (1 %)	3 (2 %)
Gastro-enterostomy aperture patent	3 (2 %)	4 (3 %)
Part of colon resected	3 (2 %)	Nil
Gall-stones	2 (1 %)	3 (2 %)
Catarrhal jaundice	1 (1 %)	Nil
Malignant tumour of pancreas	1 (1 %)	Nil
Liver abscess	1 (1 %)	Nil
Stricture of oesophagus	1 (1 %)	Nil

These figures lend no support to the view expressed by Rovsing (2), Lane (3), and Jordan (4), that visceroptosis is especially likely to be associated with gastric and duodenal ulceration. Also, as Walton (5) points out, ptosis is more common in women than in men, whereas the reverse is true of chronic gastric and duodenal ulcers. On the other hand, both pulmonary tuberculosis and arthritis occurred about twice as often in the gastroptotic patients as in the others, and these figures, though small in number (twelve patients with arthritis and eleven with tuberculosis), so far as they go support Lane's thesis that prolonged toxaemia due to the stasis of the gastro-intestinal contents commonly found with visceroptosis lowers the patients' resistance and renders them more liable to other infections.

Although appendicitis was comparatively seldom diagnosed in the gastroptosis cases, some abnormality was found more often than in cases with a more highly situated stomach, as will be seen later. It has been suggested by Brown (6) that in cases of visceroptosis a chronic appendicitis occurs, which is only one part of a low grade inflammatory process, including the terminal ileum, caecum, ascending colon, and sometimes the first part of the transverse colon.

Our cases cannot be regarded as affording evidence either for or against this view.

Aetiology.

The word gastroptosis, for the sake of brevity, will be used to signify dropping of the lower border of the stomach to a point 10 cm. or more below the summits of the iliac crests, unless it is otherwise stated.

General incidence. In the series of 684 cases, gastroptosis occurred 150 times, a general percentage incidence of 22.

Sex incidence.

Of 425 men examined 56 (11 per cent.) showed gastroptosis.
Of 259 women examined 94 (36 per cent.) showed gastroptosis.

Age incidence.

Of 266 persons under 40 years of age 51 (19 per cent.) showed gastroptosis.
Of 418 persons of 40 years or more 99 (24 per cent.) showed gastroptosis.

[The comparative ages of the 150 patients with gastroptosis were as follows:

The youngest was 9 years old.

From 10 to 20 years	. . . .	4 patients.
From 20 to 30 „	. . . .	12 „
From 30 to 40 „	. . . .	43 „
From 40 to 50 „	. . . .	54 „
From 50 to 60 „	. . . .	31 „
From 60 to 70 „	. . . .	4 „
From 70 to 80 „	. . . .	1 patient.]

Age and Sex.

Of 155 men under 40 years of age 17 (11 per cent.) showed gastroptosis.
Of 270 men of 40 years or more 39 (14 per cent.) „ „
Of 111 women under 40 years 34 (31 per cent.) „ „
Of 148 women of 40 years or more 60 (41 per cent.) „ „

Child-birth.

Of 146 women who had not borne children 50 (34 per cent.) showed gastroptosis.
Of 113 women who had borne one or more children 44 (39 per cent.) showed gastroptosis.

Number of Children.

Of 60 women who had borne 1 or 2 children 20 (33 per cent.) showed gastroptosis.

Of 53 women who had borne 3 or more children 24 (45 per cent.) showed gastroptosis.

Age and Child-birth.

Of 87 nulliparae under 40 years of age 28 (32 per cent.) showed gastroptosis.

Of 59 nulliparae of 40 years or more 22 (37 per cent.) „ „

Of 24 mothers under 40 years of age 6 (25 per cent.) „ „

Of 89 mothers of 40 years or more 38 (43 per cent.) „ „

Heredity. Information on this point is, as a rule, unobtainable, as X-ray observations have only been extensively carried out during the past decade. In only two of my cases was there a family history of gastroptosis. In 50 cases (33 per cent.) there was a family history of dyspepsia; in 15 (10 per cent.) of neuropathic tendency; in 15 (10 per cent.) of tuberculosis; in 14 (9 per cent.) of cancer; and in 7 (5 per cent.) of nephritis.

Previous illnesses (excluding the 50 cases with complications mentioned above). In 23 of the 100 cases the patient dated the symptoms from an attack of some acute specific fever such as typhoid or scarlet fever; in 8 from an attack of appendicitis; in 10 from a period of severe mental and physical strain; in 9 from a confinement; in 6 from an abdominal operation; in 4 from a prolonged and acute attack of diarrhoea; and in 2 from a severe fall and from syphilis respectively.

In view of a possible orthopaedic origin it is of interest to note that one patient dated his digestive symptoms from the onset of spinal curvature at the age of 17.

Mode of life. The condition is by no means confined to individuals who have led sedentary lives with insufficient exercise. Indeed, in the case of some women gymnastic exercises and games, when carried to excess, seem to have had a considerable influence in determining the occurrence of symptoms. For example, the young woman of 22, whose stomach is shown in Plate 3, Fig. 97, had led a healthy, vigorous, outdoor life, with plenty of golf, riding, and other exercise. Incidentally, it is of interest to note that in her case after two months' medical treatment the lowest point of the stomach had risen from 11 to 5 cm. below the iliac crests, so that apparently over-exertion had played a part in increasing the ptosis as well as in bringing on the symptoms.

Build. Of the uncomplicated cases of gastroptosis, in men the average weight was 9 st. 8½ lb., and the average height 5 feet 10 inches. In women the average weight was 8 st. 3½ lb., and the average height 5 feet 5½ inches. (The patients were weighed when in nightgown or pyjamas and dressing-gown.)

Hutchison and Rainy (21), in a table compiled from extensive statistics, state that in the case of an individual 5 feet 10 inches in height the minimum weight compatible with good health is 9 st. 9 lb. In the case of an individual 5 feet 6 inches in height the corresponding minimum weight is 8 st. 2 lb.

It is of interest to compare some of these results with the conclusions reached by Levy and Kantor (16), who analysed a series of cases in which the stomach was dropped to a level situated more than 2·5 cm. below the iliac crests.

Such a comparison would seem to show that:

1. Men and women are almost equally liable to slight dropping of the stomach, but it is mostly among women that one finds the extreme cases.

2. In the case of slight degrees of dropping, young people are more likely to complain of symptoms than are their elders, but in the case of extreme degrees the reverse holds good.

3. In the cases both of slight and of severe dropping the incidence is approximately equal in married and in single women, but extreme dropping is found rather more often in the former and slight dropping in the latter.

Summary of Aetiological Points.

The above figures may be summarized by saying that in these cases:

1. Approximately one-fifth of the patients complaining of digestive trouble were the subjects of severe gastroptosis.

2. The condition was rather more than three times as common in the women as in the men.

3. A greater number of persons with severe gastroptosis, both men and women, complained of digestive symptoms in later life than in youth, but the condition was in a few cases observed in children and adolescents.

4. Severe gastroptosis was about equally common in the mothers and in the women who had not borne children.

5. It was rather more common in the mothers of several children than in the mothers of one or two.

6. A greater number of both nulliparae and of multiparae with severe gastroptosis complained of digestive symptoms in later life than when young, especially in the case of the multiparae.

7. A family history of digestive trouble was elicited in a third, and of neurosis, cancer, and tuberculosis each in a tenth, of the cases of severe gastroptosis.

8. In over one-half of the cases the abdominal symptoms were said to have dated from either an acute fever, an attack of appendicitis, an abdominal operation, a confinement, or a period of mental and physical strain. In the case of women, and possibly men also, excessive exercise may both bring on symptoms and exaggerate the ptosis.

9. The persons with severe gastroptosis were, on an average, emaciated to the maximum degree considered compatible with good health.

Symptoms.

Of the 100 patients with uncomplicated gastroptosis, the symptoms of which complaint was made on admission were as follows:

Symptom.	Percentage of Gastroptosis Patients by whom Complaint was made.
Constipation	67
Abdominal discomfort	53
,, ,, relieved by alkalis	4
,, ,, ,, ,, food	4
,, ,, ,, ,, passing flatus	4
,, ,, ,, ,, purgatives	3
,, ,, ,, ,, lying down	2
,, ,, ,, ,, support of belt	1
Flatulence	45
Loss of energy	44
Abdominal pain	43
,, ,, relieved by lying down	3
,, ,, ,, ,, alkalis	3
Loss of weight	36
Headache	31
Nausea	24
Depression	24
Pain in the back	19
Insomnia	18
Joint pains with or without arthritis	17
Susceptibility to cold	15
Loss of appetite	14
Bad taste	13
Vomiting	13
Abdominal distension	12
Acid eructations	12
Palpitation	11
Nervous irritability	7
Diarrhoea	6
Bad dreams	5
Vertigo	4
Sleepiness after meals	3
Splashing in the stomach	3
Heartburn	3
Dry mouth	2
Sour mouth	2
Hunger	2
Thirst	1

Comments.

Constipation is thus the rule, being a cause of complaint in nearly three-quarters of the cases.

A complaint of constipation is not always borne out by determination of the rate of passage of a barium meal; yet in these patients it was shown to be justified by X-ray examination, delay of an opaque meal in the colon or rectum being seen to occur in approximately the same individuals.

The *pain or discomfort* so often experienced was usually felt either in the epigastric and umbilical regions, in the right iliac fossa, or in both these regions; less often in the left iliac fossa. In a few cases it was undoubtedly associated with hyperacidity, seeing that it was relieved by alkalis or food, and in others with flatulence.

In most of the remaining cases it was the dull heavy pain so often associated with constipation, and was often relieved by the castor oil given as a preliminary to X-ray examination before any treatment by rest and massage had been started.

During the examination, when no purges could be given, the pain grew

worse again, and would often persist to some extent after complete rest had been started until, by means of enemas, glycerine suppositories, and massage, assisted perhaps by paraffin, a regular daily action of the bowels was obtained, when it would be completely relieved. So frequently does this happen that I am being led to the conclusion that the pain occurring with uncomplicated gastroptosis is in the main not of gastric origin at all. If it were, one might expect that rest in a recumbent position with the feet raised, together with a suitable diet, would relieve it quite independently of the state of the bowels.

With regard to the complaint of *flatulence* in about half of the cases, it is of interest to note that Leven (15), in a monograph on aerophagy, mentions gastroptosis as likely to irritate the solar plexus and so set up deglutition movements. In the case of those patients whose gastric juice was of normal or increased acidity (79 per cent. of those examined) aerophagy is a more probable explanation of the gastric flatulence than the fermentation of which patients often speak.

Loss of energy, loss of weight, and *headaches*, occurring in ⅓ to ½ of the cases, and *susceptibility to cold*, are all features of toxaemia and of consequent subnutrition which leads to a general loss of tone and overstrain. Boas (13) attributes the subnutrition to a fear of eating because of the consequent pain or discomfort. Constant underfeeding leads to a loss of appetite, and a vicious circle is thus formed. This is no doubt the case in some patients, but in the large majority of those under consideration the pain bore no constant relation to meals, and the patient, in endeavouring to increase his bodily comfort, was concerned rather with his excreta than with his ingesta.

The fact that only one patient complained of *thirst* is of interest, as Boas (13) mentions this absence of thirst in simple gastroptosis as distinguishing that condition from pyloric stenosis in which thirst is a prominent symptom.

Pain in the back, present in a fifth of the total number of cases, is stated by Boas (13) to be especially typical of gastroptosis when it occurs on sharp movements of the body. This was rarely the case in my patients.

Diarrhoea *per se* was rare, occurring in only six cases: in another twelve it alternated with constipation and was probably secondary to the latter.

Briefly stated, the prominent symptoms on admission were, first and chiefly, constipation; secondly, pain or discomfort coming on at irregular times, and situated in the upper abdomen or right or left iliac fossa. The pain and discomfort and the constipation were, as a rule, closely associated. Thirdly, flatulence, mostly intestinal and associated with constipation, but often gastric and possibly due to aerophagy. Fourthly, a group of symptoms suggestive of toxaemia, such as loss of energy, headache, depression, insomnia, anorexia, bad taste, joint pains (with or without actual arthritis), susceptibility to cold, and emaciation.

In other words, complaint was made of constipation and the symptoms usually attributed to a resultant alimentary toxaemia.

Radiographic Examination Results.

In considering the general shape of the stomach 149 cases were reviewed, the one omission consisting of a case in which the organ was pushed down by a tumour.

In order to avoid vitiation of any deductions from inclusion of cases complicated by extraneous lesions I have left out of account the 50 patients, referred to in the section on 'Complications', who were the subjects of other lesions there set forth. Patients with arthritis were not excluded. 100 uncomplicated cases then remain, and X-ray observation of these gave the results tabulated.

TABLE II. *Radiographic Findings in 100 Uncomplicated Cases of Gastroptosis.*

Sign.	Percentage of Patients presenting it.
Stomach hypertonic	1
,, hypotonic	71
,, of normal tone	28
,, deformed (as shown by irregular outline)	10
,, delay (material present after 5 hours)	57
,, emptied in 5 to 6 hours	30
,, ,, ,, 6 to 7 hours	9
,, ,, ,, 7 to 8 hours	3
,, ,, ,, 8 to 9 hours	7
,, ,, ,, 9 to 10 hours	2
,, took over 10 hours to empty	6
,, emptied in under 4 hours	5
Gastric peristalsis active	68
,, ,, feeble	30
,, ,, apparently absent	2
Intermittent pylorospasm	8
Pylorus persistently contracted	2
,, tending to gape	6
,, showed irregularity of outline	9
Duodenal cap showed irregularity of outline	18
,, ,, contracted	5
,, ,, dilated	2
Second part of duodenum kinked	1
Ileal stasis (material present 4 hours after stomach emptied) (22)	42
Terminal ileum immobile on manipulation	18
,, ,, contracted	2
Caecum lying in pelvis	2
,, dilated	3
,, immobile on manipulation	27
Appendix filled and emptied normally	41
,, ,, partially	9
,, was immobile on manipulation	6
,, showed stasis of contents	24
,, ,, intermittent localized spasm	2
,, ,, irregularity of outline	6
,, did not admit any barium	15
,, had been previously removed	16
,, was retrocaecal	4
One or more parts of the colon dropped	47
Transverse colon only dropped	29
,, ,, with both hepatic and splenic flexures dropped	8
,, ,, and hepatic flexure dropped	8
Hepatic flexure only dropped	2
Colon delay (material present later than 48 hours after meal had been taken)	66
Rectal delay (material reached rectum, but was not evacuated, and there was no desire to defecate)	17

In the following table some of the above results are compared with those obtained on examining 100 other patients in Duff House, all of whom complained of alimentary symptoms and were consequently X-rayed, and in whom the stomach was found to be in an approximately normal position. The cases were taken haphazard, except that they do not include any in which lesions mentioned in the section on 'Complications', such as ulcer or growth, were diagnosed.

TABLE III. *Comparison of X-ray Findings in 100 Cases of Gastroptosis and in 100 Cases with Stomach in Normal Position.*

Sign.	Percentage in Extreme Gastroptosis.	Percentage with Stomach in Normal Position.
Stomach hypotonic	71	9
,, hypertonic	1	10
Intermittent pylorospasm	8	5
Pylorus persistently contracted	2	2
Delay in stomach	57	36
Contraction of duodenal cap	23	11
Ileal stasis	42	32
Appendix admitted little or no barium, or was immobile, or showed stasis of contents, spasm, or irregularity, or had been removed, or showed more than one of these signs	59	46
Coloptosis	47	10
Colon delay	66	45

Comments.

Under the heading of 'Complications' I mentioned that active *gastric or duodenal ulceration* was diagnosed in 8 per cent. of the gastroptosis cases and in 11 per cent. of the others. Now if ulceration is as common in people whose stomachs are not dropped, gastroptosis is clearly not the main determining factor in the majority of cases. The accuracy of this statement receives further support if the percentage of cases in which there is presumptive evidence of old ulceration (such as irregularity or contraction of the duodenal cap or pylorus) is, in the case of each class, added to the corresponding figure above. The figures will then be 31 per cent. and 27 per cent. respectively, leaving a balance so small as to be negligible.

On analysing two series of 30 cases of duodenal ulcer and of gastric ulcer respectively, it is found that X-ray examination showed *stasis in the ileum or colon* or both in only 50 per cent. of the patients in both series.

Rather less than one-third of the dropped stomachs were of normal *tone*, while over two-thirds were hypotonic. Hypotonus was thus the rule in the severely dropped stomachs, but was found in only a tenth of the more highly situated ones.

Delay in the passage of the gastric contents was frequent, and was sometimes extreme. It occurred more than half as often again as in the case of the more highly situated stomachs. If, in both these groups, the cases of pylorospasm and pyloric and duodenal contraction (without definite evidence of ulcer)

are ruled out, delay still was more frequent in the dropped stomachs, the proportions being 1⅓ to 1.

Feeble peristalsis was only seen in about half of the cases in which there was gastric delay.

Although peristalsis and normal tone are controlled by the same nervous mechanism, and are often mutually dependent, it is found that either may be present without the other.

Intermittent *spasm of the pylorus* may occur in association with hyperacidity of the gastric juice and, though suspicious, does not necessarily indicate ulceration. The *contracted pylorus* occurring in 2 per cent. of the cases was due either to contraction after ulceration, or to the dragging of adhesions, or to congenital stenosis. The pylorus is prevented from kinking by the nature of its peritoneal attachments.

Irregularity of outline and contraction of the duodenal cap occurred twice as often in dropped as in more highly situated stomachs. Stasis in the ileum and in the colon was more frequently found with the extremely dropped stomachs than with the more normally placed ones, in the proportion of 1¼ to 1 and 1½ to 1 respectively.

It seems reasonable to regard the *stasis occurring in the small and large intestines,* as well as that in the stomach and that so often found in the appendix, as due to a general lack of tone involving the whole alimentary canal.

The question arises in this connexion as to what is the causal relationship between the dropping, the loss of tone, and the stasis? First, it is clear that dropping of the viscera can exist without any delay or apparent loss of tone. For example, Plate 2, Fig. 8, shows a dropped stomach of normal tone which emptied in four hours. Figs. 13, 16, 35, and 43 show other examples.

But it is difficult to decide whether loss of muscular tone or stasis comes first. Either condition may be present without the other. For example, Plates 3 and 4, Figs. 79, 81, 127, and 135, show hypotonic stomachs which emptied in normal time, while Plate 2, Fig. 4 shows a stomach of normal tone which contained barium more than six hours after the meal.

After X-ray observations have been made over a period of many years it may be established, by viewing the same patient repeatedly, that loss of tone precedes the stasis in a majority of cases. Meanwhile, we can only recognize that either or both may be present, and that they tend, in the latter case, to assist each other.

Hypertonus was nine times more common among the stomachs situated at a higher level than among those that were dropped.

Dropping of the flexures, by lessening the kinking at those points, should, *per se,* assist the passage of the contents through the colon.

The *kink 2 or 3 inches from the end of the ileum,* with proximal dilatation, as described by Lane, was seen in three cases, and the duodenal kink described by him was seen once.

The *dilated dropped caecum* described by Wilms (9) and found by Walton (5) in his cases of visceroptosis was seldom seen. In this connexion I would point

out that when the caecum is situated in the pelvis its X-ray shadow is more likely to be exaggerated in size and distorted than when it lies in the iliac fossa. (See Method employed in Radiological Examination, Figures in text.)

The condition described by Hurst (8) as the *orthostatic hour-glass stomach* was seen in two cases.

Irregularity of the stomach outline, seen in one-tenth of the cases, might be caused by cicatricial contraction following old ulceration, by adhesions, or by pressure from other viscera distended with gas.

The solitary example of a hypertonic and severely dropped stomach occurring in the series of 150 cases (Plate 2, Fig. 1) was seen in a single woman 59 years of age. Her symptoms, dating from a mental shock received nine years before admission, were pain in the back and limbs, headache, vertigo, flatulence, constipation, and obstinate anorexia. On examination there was great emaciation, the teeth were defective, and there was pyorrhoea; the gastric acidity was normal, and there was moderate anaemia. The stomach emptied in under 3½ hours, and the pylorus and duodenal cap were normally filled. The appendix was retrocaecal and showed stasis of its contents, and the colon was dropped and sluggish.

Summary of Radiographic Findings.

In brief, then, X-ray examination shows that the gastroptosis is only one among many indications of a general loss, or rather lessening, of tone in the gastro-intestinal musculature. The severely dropped stomach is usually hypotonic and unable to expel its contents into the duodenum in normal time, peristalsis being often feeble.

This delay is due to inefficiency of the gastric musculature, and is independent of pyloric or duodenal obstruction.

The pylorus is not, as a rule, dropped to the same extent as the fundus, so that gravity plays a part in throwing an increased strain on the muscles, which in turn become fatigued and relaxed, so that the fundus drops still farther, and thus a vicious circle is formed.

Stasis, in the ileum, or the colon, or both, is the rule, and appendicular stasis and rectal delay are often present.

Dropping of the transverse colon commonly accompanies gastroptosis, but dropping of the flexures is comparatively seldom found, especially in the case of the splenic flexure.

Evidence of an old inflammation in the region of the appendix, such as immobility of the caecum or terminal ileum owing to adhesions, is frequently discovered.

There is no evidence to show that the condition of the stomach and bowel, commonly found in gastroptosis cases, is especially favourable to the formation of gastric or duodenal ulcers.

Associated Signs: Clinical and Chemical.

As stated in the section dealing with 'Aetiology' both men and women were, on an average, considerably under weight in proportion to their height. A typical patient of either sex was tall and thin, with a rather sallow complexion, dark patches under the eyes, and cold, red extremities.

The general signs observed on examination of the 100 uncomplicated cases may be tabulated as follows:—

TABLE IV. *Signs observed in 100 Uncomplicated Cases of Gastroptosis.*

Sign.	Percentage of Patients presenting it.	
Inadequate teeth	33	
Pyorrhoea alveolaris	19	
Furred tongue	46	
Distended abdomen	12	
Tender abdomen	41	
Right kidney dropped	19	
Both kidneys dropped	6	
Liver dropped	4	
Diaphragm dropped	2	
Gastric hyperacidity	49	of 73 cases in which the gastric juice was analysed
Poverty in acid	21	
Normal acidity	30	
Pulse-rate accelerated	11	
,, slow	30	
,, normal	59	
Systolic blood-pressure abnormally high	8	
,, ,, ,, low	56	
,, ,, normal	36	
Blood deficient in haemoglobin	54	
Haemoglobin 80–90 % of normal	29	
,, 70–80 % ,,	14	
,, 70 % or less ,,	11	
Poverty in red corpuscles	24	
Leucopenia (less than 6,000 per c.mm.)	39	
Leucocytosis	7	

Comments.

The *coated tongue* found in over a third of the cases was, in many, probably due to the pyorrhoea which was present; in some of the remaining cases it may well have been due to excessive smoking or some other cause independent of the stomach.

Our records show that a coated tongue constitutes no evidence of real value as a symptom of indigestion. Vanderhoof (10) suggests as the chief causes of pronounced furring: (*a*) nasal obstruction, with mouth breathing; (*b*) absence of friction, for example, in patients on a liquid diet; (*c*) perversion of the salivary secretion, especially common in neurotic individuals.

My own experience confirms absence of friction as a cause, for our patients commonly have thickly-coated tongues when under treatment for ulcer by a modified Lenhartz diet, which involves abstention from solids for a considerable period. A coated tongue is also common in patients who are taking solid food,

but in small quantities, as for obesity. When the diet is increased the tongue becomes cleaner.

The small number of cases in which *abdominal distension* was observed is rather striking. When present, it was usually general in the recumbent position, and more or less confined to the lower abdomen when erect.

The two most common points at which *tenderness* was found on palpation were, first, at a point in or just to the left of the middle line, about two inches above the umbilicus; and, secondly, in the neighbourhood of McBurney's point in the right iliac fossa.

There is a distinct *tendency to hyperacidity* of the gastric juice, about half the cases showing this condition. At the same time, the percentage of cases in which there is a *deficiency of acid* is greater than is the case when stomachs in the normal position are concerned.

The tendency to *low blood-pressure* is probably associated with the general subnutrition, and is found in the various forms of dyspepsia.

The *anaemia* associated with half the cases was almost invariably of the chlorotic type with a colour index of less than unity. Meinert (11) found some degree of chlorotic anaemia in every case of gastroptosis, and Rostoski (12) found the stomach dropped in 26 per cent. of a series of chlorotic individuals. Boas (13) also attaches importance to gastroptosis as a cause of anaemia.

There is a definite tendency to *leucopenia*, which is probably due to subnutrition, as it is commonly found in fasting individuals (14).

In brief, then, the prominent signs on general examination were height rather above and weight distinctly below the average, sallow complexion, and cold, red extremities; and, in many cases, inadequate teeth, a furred tongue, tender abdomen, hyperacid gastric juice, low blood-pressure, and anaemia of a secondary type with leucopenia.

Treatment.

Preventive treatment consists in:

(1) Exercises and drill during childhood and adolescence, followed by regular moderate exercise in later life.

(2) An adequate diet with a sufficiency of fruit, green vegetables, and fluids.

(3) Inculcation from the first of regular habits; a daily visit to stool at the same time each day being enforced, and the importance of it being impressed upon the child when old enough to understand.

(4) Prompt treatment of any irregularity of the bowels or of dyspeptic symptoms.

Curative treatment.

A vicious circle is formed by the lack of tone in the gastro-intestinal musculature which, together with the sagging of the stomach and colon, causes stasis, this, in turn, leading to toxaemia, anaemia, and malnutrition, and so to a further decrease in tone. This circle must be broken at as many points as possible, and experience leads me to believe that its most vulnerable spot is the intestinal

stasis. When this is relieved the subjective symptoms often temporarily clear up even apart from treatment in other directions.

1. A suitable régime for the relief of constipation (if present).

(*a*) *Diet.* An ample lacto-vegetarian diet, such as that recommended by Boas for constipation, has been found most useful in our experience. For example:

7 a.m.	½ oz. of paraffin in 2 oz. of warm milk.
8 a.m.	Coffee and milk; 1 tablespoonful of milk sugar. Wholemeal bread; butter; honey or marmalade.
10.30 a.m.	A glass of butter-milk; wholemeal bread and butter.
1 o'clock.	Fish (cooked any way); butter sauce; salad and dressing. Compote of fruit; cream; toast and butter.
4 o'clock.	Coffee, with milk or cream; marmalade. Wholemeal bread (toasted, if desired) and butter.
Dinner.	Vegetable soup; some egg dish (poached, scrambled, or omelette) with vegetables or fruit. For instance, may have jam or jelly omelette, or omelette *aux fines herbes*; cream cheese; wholemeal bread; butter.

On going to bed paraffin ½ oz. in warm milk 2 oz., and raw fruit according to season. Water, or soda-water, with lime-juice, if desired, is taken with meals.

If there is gastric hyperacidity an ounce of olive oil is given half an hour before lunch and dinner, or, if this is not well borne, a switched egg. Hot water is taken between meals.

(*b*) Massage of the abdomen, preferably under the hot douche, is given on alternate days, the radiograms being consulted and special attention being paid to those parts where the stasis is most evident.

(*c*) Electrical treatment may be applied on the days alternating with those of massage. The poles are placed, one over the lumbar spine and the other on the anterior surface of the abdomen. They should be large, and the abdominal electrode is moved over the whole surface of the abdomen for a period of five to ten minutes. An alternative method is to administer rhythmically interrupted currents by means of the Bergonié chair.

2. The malnutrition is combated by rest in bed, either in a room, or, if the weather permits, in a hut out of doors, provided that the necessary privacy and warmth can be secured. Every possible effort should be made to prevent worry or mental strain of any kind. The rest prevents waste of energy, and the tranquil existence is likely to improve the psychic secretion of the gastric juice if that is lacking. The patient is thus enabled to derive the maximum benefit from his diet, so that the weight rises, the anaemia improves, and the tissues are well nourished.

3. The malposition of the viscera, which aggravates though it does not cause the gastric and intestinal stasis, and may prevent the patient from deriving full benefit from the above measures, is temporarily rectified, wholly or partially, by

keeping the patient recumbent and raising the foot of the bed on blocks 8 inches high. At the end of treatment the stomach may or may not be found to have been permanently raised to a higher level, but the rate of emptying has almost invariably improved.

4. In most cases the treatment described above will prove sufficient, and the symptoms will be relieved. Sometimes, however, certain symptoms will prove very resistant, and will need additional measures.

For example, in order to overcome the constipation it may be at first necessary to wash out the lower bowel on alternate days, afterwards gradually lengthening the intervals.

The anaemia may be so severe as to call for the addition of meat to the diet and hypodermic or intramuscular injections of cacodylate of soda or some other haematinic.

For the pain or discomfort caused by gastric hyperacidity, hydrated magnesia should be given in small doses when required.

If, on the other hand, the gastric juice is found to be deficient in acid, or if there is achylia, hydrochloric acid, with or without pepsin, is indicated twenty minutes after each meal.

If the stomach delay is extreme gastric lavage should be carried out daily, an hour before the evening meal. Great nervousness or irritability may call for bromides.

5. Treatment must be carried on for some time after all symptoms have been relieved, and until the weight is substantially increased. In any case a minimum period of two months is necessary if the result is to be satisfactory.

6. The patient is then gradually allowed to resume a normal mode of life, but should be warned of the dangers appertaining to any excessive mental or physical strain. A suitable diet should be prescribed, and rests on a bed advised for an hour before each of the two principal meals of the day. Attention must be paid to the bowels, and paraffin taken if necessary: on no account must they again be allowed to become constipated. Suitable mild exercises will be useful at this stage, especially those calculated to strengthen the muscles of the abdominal wall.

In the case of young people, in addition to the above, a course of exercises designed to improve the skeletal muscles and body-shape should be arranged, special attention being given to those which improve the lumbar curve and widen the lower thorax.

Abdominal belts, of which many forms are in the market, are occasionally of some use after the completion of a course of medical treatment, or in the event of such a course being impossible for pecuniary or other reasons.

They are especially indicated in the case of elderly patients with great dropping of the viscera and long-standing constipation or gastric symptoms. Such a belt, however, must be chosen with great care and should be applied before rising from the recumbent position.

Whenever possible a barium meal should be given and the stomach viewed

with the belt in position. I have been impressed with the importance of this last point by a series of X-ray observations in the case of a number of patients wearing a great variety of belts. In most cases the stomach was not raised to any appreciable extent, and in some it was actually pushed downwards.

A note on operative treatment. As Walton (5) explains, operative treatment must be regarded, not as a means of cure, but as an adjunct to other measures. He gives as indications for it, first, a late stage of the condition when the bands or membranes have undergone secondary shortening, so that they prevent the viscera from returning to their normal position; secondly, the presence of neurasthenic symptoms which prevent the collaboration of the patient in the treatment.

Many different operations have been devised, for example:

1. *Division of the membranes and bands* in order to overcome kinking and obstruction. Gray and Anderson (17) and others report good results from this procedure, but cases have occurred in which adhesions were found and peritonitis followed the operation, and Walton (5) has found in a series of cases that temporary relief was followed by a return of symptoms.

2. *Fixation of the prolapsed viscera* on the assumption that the ptosis is the primary change. Caecopexy and colopexy have been advocated, and many attempts have been made to fix the dropped stomach in a better position; for example, Duret, in 1896, described an operation which plicated and fixed the lesser curve of the stomach (18); Rovsing stitches the serous coat of the anterior surface of the stomach to the anterior abdominal wall, scarifying the apposed serous surfaces; Coffey passes sutures through the parietal peritoneum, the gastrocolic omentum, and the great omentum, so that when tied they raise and fix the colon and greater curvature of the stomach.

All operations for the fixation of viscera are open to objection on the ground that, first, fixation may interfere with normal action; secondly, they are often fruitless because the adhesions formed are drawn out as attenuated bands; thirdly, if one viscus only is fixed a further band may be formed at the point of fixation round which kinking of the unfixed viscera may take place.

Walton (5) finds that after such operations the symptoms have persisted, and X-ray examination has shown that the ptosis is far from being cured.

3. *Attempts to refashion the abdominal cavity,* thus remedying the narrowing of the upper, and widening of the lower abdomen. Coffey and Rovsing have devised plastic operations for this purpose, but according to Walton's experience the after-results are invariably poor, and not uncommonly there is a ventral hernia.

4. *Attempts to overcome stasis,* of which the earliest:

(*a*) was plication of the viscera, a procedure which has been almost entirely abandoned.

(*b*) Appendicostomy, with a view to washing out the lower bowel, has been advocated by Mummery (19). The whole of the lower bowel, from rectum to caecum, can be efficiently irrigated by the Plombières method, as we have repeatedly demonstrated by X-ray examination after a barium enema, so that a

major operation, not devoid of risk, for this purpose would not appear to be justifiable.

(*c*) Ileocolostomy and colectomy as practised by Sir Arbuthnot Lane, followed by many other surgeons, for chronic constipation and for the mastitis, arthritis, cholelithiasis, and gastric ulceration which he attributes to the resulting auto-intoxication.

Lane and his co-workers have recorded remarkable results in such cases, but opinion on the subject is very divided.

As regards visceroptosis, my own figures do not show that mastitis, gallstones, or gastric ulceration are more frequently met with in the subjects of this condition than in others, and as regards constipation in general, medical treatment on the lines described above, carried out for a sufficiently long period, offers such excellent chances of relief that I should be most reluctant to advise an operation of such severity, especially as I have seen patients whose condition has been rendered worse thereby. Hurst has met with similar cases (20), and the experience of surgeons, other than Lane, has been so varied as to be inconclusive.

General Conclusions.

1. Severe gastroptosis is frequently met with in persons of both sexes who complain of digestive symptoms.

2. In these cases it was several times more common in women than in men, but this predominance had little or no relation to childbirth, as the condition was found almost as frequently in childless women as in mothers.

3. A low position of the stomach is commonly associated with a tall spare build, especially in the case of men.

4. Severe gastroptosis may be unaccompanied by any symptoms which could reasonably be attributed to it.

5. Gastroptosis is only one manifestation of a general condition referred to as the *habitus asthenicus* (Stiller) and *habitus ptoticus* (Walton) by various authors.

Both of these terms are open to objection on etymological grounds. The first is a hybrid of both Greek and Latin origin. The second, also a hybrid, does not indicate the tendency to a general loss of tone which would seem to be the most important pathogenic factor in operation. I would suggest as more descriptive and etymologically correct the term 'Hypotonic diathesis' (from the Greek *ὑπό* under, *τείνω* I stretch; *διά* asunder, *τιθέναι* to place). This I would define as a particular condition or habit of body predisposing to a loss of tone in the musculature of the alimentary canal, and commonly associated with a low position of the abdominal viscera.

In the production of the derangements of function caused by the diathesis, dropping of the stomach plays a comparatively unimportant rôle, as is proved by the complete and often permanent restoration of gastroptotic patients to health, without alteration of the position of the stomach in the erect position as shown by X-ray examination.

6. That the hypotonic diathesis may be congenital is indicated by the discovery of severe gastroptosis in young children.

7. Such children may reach adult life, and even old age, without suffering any inconvenience, provided that they lead an equable existence and are subjected to no great strain by severe illness, overwork, shock or worry, a rapid succession or a large number of confinements, or other means.

8. In the event of the occurrence of such a strain, an individual with the hypotonic diathesis has a tendency, greater than in the case of a normal individual, to develop a certain train of symptoms.

9. The fact that women are liable to the strain of menstruation in addition to those usually bringing on the group of symptoms in men may explain the greater frequency of the syndrome in the former sex.

10. When a person with this diathesis is subjected to such a strain a vicious circle is set up which, if not broken, seriously undermines his health and resisting powers, and renders him especially susceptible to infection by pathogenic organisms, such as the tubercle bacillus, the organisms causing pyorrhoea, and others. A general lack of tone in the musculature of the alimentary canal manifests itself, together with an alteration in the gastric (and probably intestinal) secretions. There is a tendency to stasis in the stomach, ileum, appendix, and large intestine; and, once started, this delay in the passage of the contents is assisted by an altered configuration of one or more of these viscera. The increasing stasis frequently results in ill health attributed to absorption of toxins, as shown by anaemia with a sallow complexion, loss of weight, a fall in the blood-pressure, and symptoms, such as languor, anorexia, headache, depression, insomnia, and susceptibility to cold.

The malnutrition of the tissues which results, aggravated by distaste for food and alterations in the digestive secretions, leads to a further weakening of the gastro-intestinal musculature, and still greater stasis of the contents.

The symptoms vary greatly, and are not always in accordance with the physical signs discovered.

Generally speaking, they roughly correspond with the section of the alimentary canal in which stasis predominates. Thus intestinal delay is associated with constipation, sometimes alternating with attacks of diarrhoea and accompanied by the passage of mucus, and with irregular dull discomfort or pain, mostly in one or other of the iliac fossae or in the upper abdomen; there may also be symptoms suggesting toxaemia.

With gastric delay there may be eructations of gas and sour liquid, nausea, and possibly vomiting, often with epigastric or umbilical pain and with tenderness at a point in the middle line above the navel.

In the case of the stomach, symptoms may, of course, be modified according to the composition of the gastric juice.

It must be recognized, however, that stasis may be present in either situation without causing subjective symptoms.

Some evidence of intestinal stasis, either an X-ray finding or a history of

constipation, was obtainable in 91 of my 100 uncomplicated cases; and, of the remaining nine patients, seven complained of no digestive symptoms, but were examined radiographically in the hope of discovering a cause for headache, high blood-pressure, or some other condition not necessarily connected with the digestive organs.

An adequate dietary, sufficient (but not excessive) exercise, and careful attention to the bowels during childhood and adolescence are the most important points in prophylaxis. In any case of obstinate constipation or indigestion X-ray examination after a barium meal should be made, if possible. By this means the diathesis may be recognized before the vicious circle, described above, is fully set up, and the symptoms relieved with comparative ease before the general health is impaired.

When once the condition has reached the stage when the various derangements of function react upon each other with progressively evil effects, a course of medical treatment, extending over several months, should be carried out.

The constipation is relieved by means of a lacto-vegetarian diet, paraffin, and abdominal massage with, perhaps, electrical treatment, and, if very severe, intestinal lavage. Nutrition is improved by rest, diet, and absence of worry, bromides being given if there is great irritability or insomnia. Haematinics are given if the anaemia is severe, antacids if there is gastric hyperacidity, and hydrochloric acid and pepsin if there is poverty of the gastric juice. In cases of prolonged gastric delay, daily lavage of the stomach will assist that organ to recover its tone.

In order to obviate the effect of dropping of the viscera in assisting in the production of stasis, the patient rests on an inclined plane with the feet raised.

If such a régime is possible the prognosis is good as regards the relief of symptoms and, provided the after-treatment advised is also carefully carried out, as regards the probability of a relapse.

The tissues may be subjected again to some severe stress, but the musculature of the alimentary canal will now be in a more resistant condition; and suitable treatment, based on recognition of the diathesis, can be instituted without delay so that the attack will either be prevented altogether or aborted at an early stage.

In conclusion I wish to express my thanks to Dr. Spriggs for his encouragement and advice during the progress of this study.

I have made free use of notes on cases by Drs. Pickering, Long, and Mary Watson, to whom my thanks are due; also to Messrs. Marxer and Leigh, to whose valuable observations, incorporated in the paper, I have referred above.

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B. Reduced radiograph showing hypotonic dropped stomach. Anterior superior iliac spine (*a*) and top of symphysis pubis (*b*) indicated by dots. In measuring extent of dropping a horizontal line is drawn through (*a*), and a vertical line through (*b*). Measurements are then taken by means of a scale with zero placed at the point of intersection of the two lines.

A. Reduced radiograph showing stomach in normal position. The white dot indicates the anterior superior spine of the left ilium.

PLATES 2, 3, 4.

Photographs of Indian ink drawings by the author of the stomach shadows

The 150 stomachs which form the basis for the present investigations are shown, and the diagram of part of the skeleton in each photograph shows approximately the degree of dropping and the relation of the different parts of the stomach to the bony points mentioned in the text.

The upper of the two numbers over each drawing has no significance for the purpose of this paper.

The stomachs are shown as viewed when in the erect posture immediately after the barium meal, being roughly arranged so that those showing most loss of tone are placed last.

Thus the single example of definite hypertonus in a dropped stomach is shown in Fig. 1.

Stomachs of normal tone—Figs. 2–12, 14–27, 29–30, 32–34, 36–43, 45–49.

Hypotonic stomachs – Figs. 13, 28, 31, 35, 44, 50–150.

Orthostatic hour-glass stomachs—Figs. 148–9.

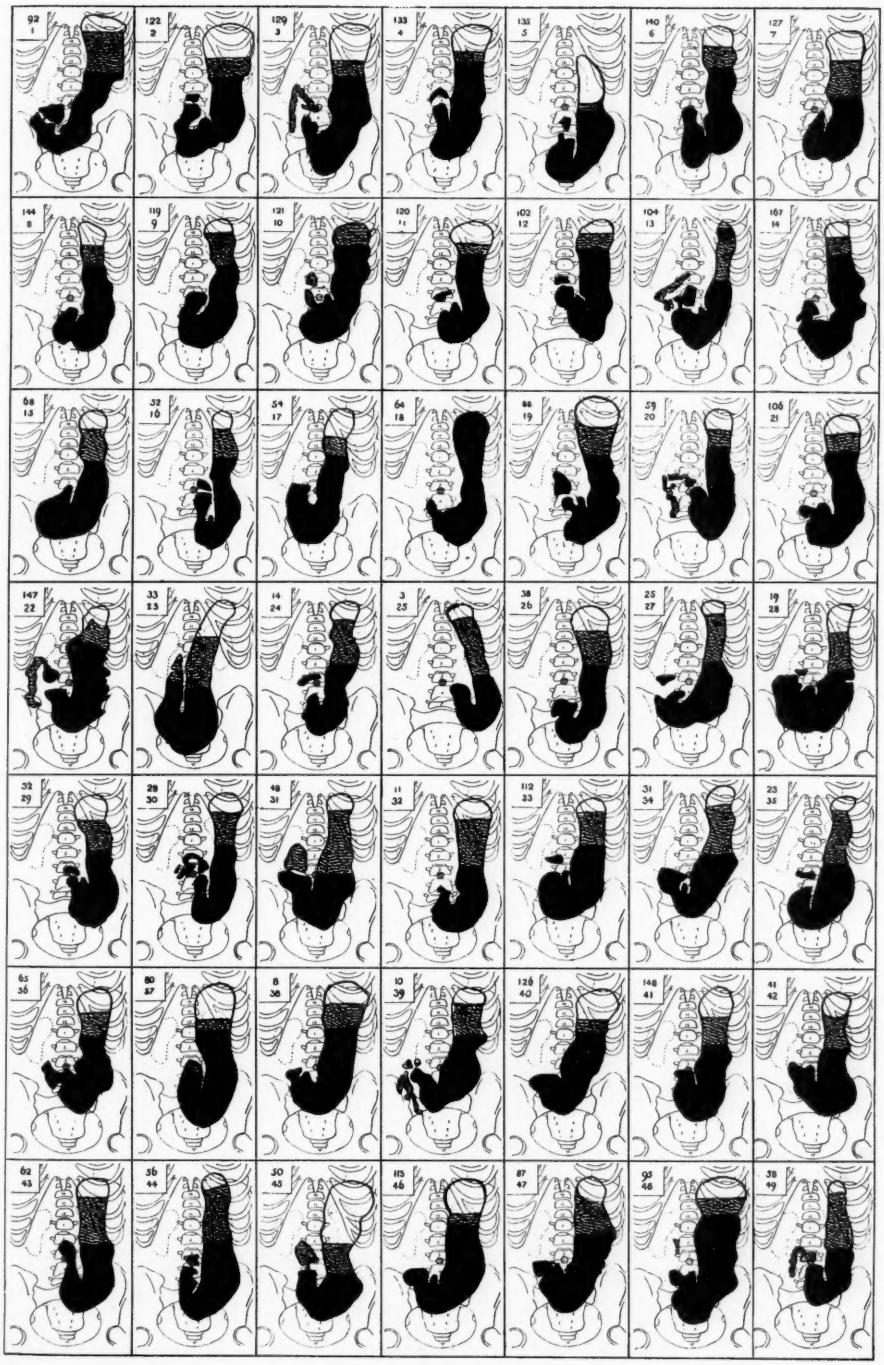
Hour-glass stomach caused by pressure by a pancreatic tumour – Fig. 150.

Spasmodic stricture of the oesophagus present—Fig. 134.

Gastro-enterostomy cases – Figs. 2, 41, 114. The stoma is not in evidence in the photographs.

Adhesions due to subphrenic abscess – Fig. 22.

In some cases barium has at once entered the duodenal cap, and this is shown.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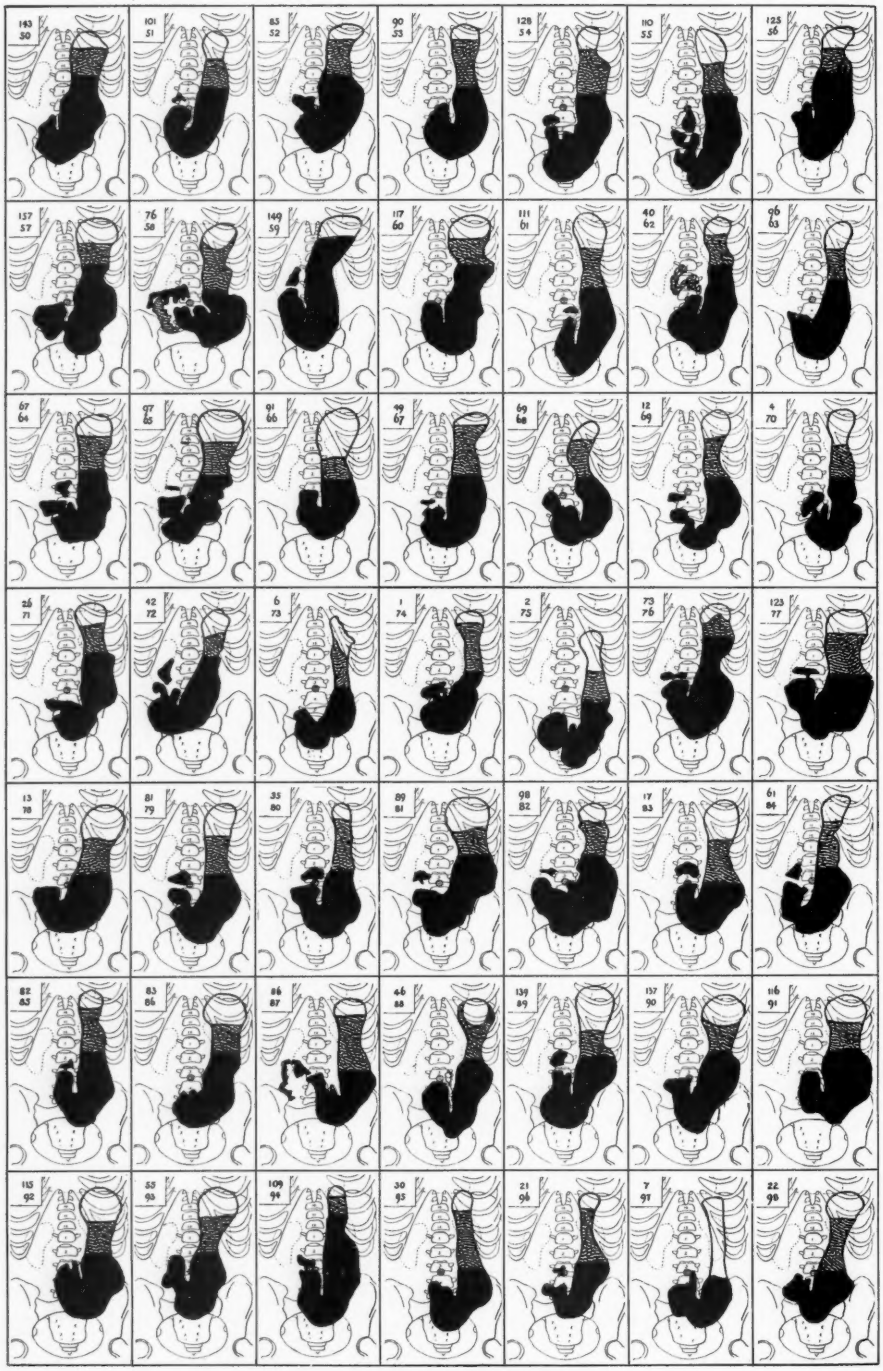
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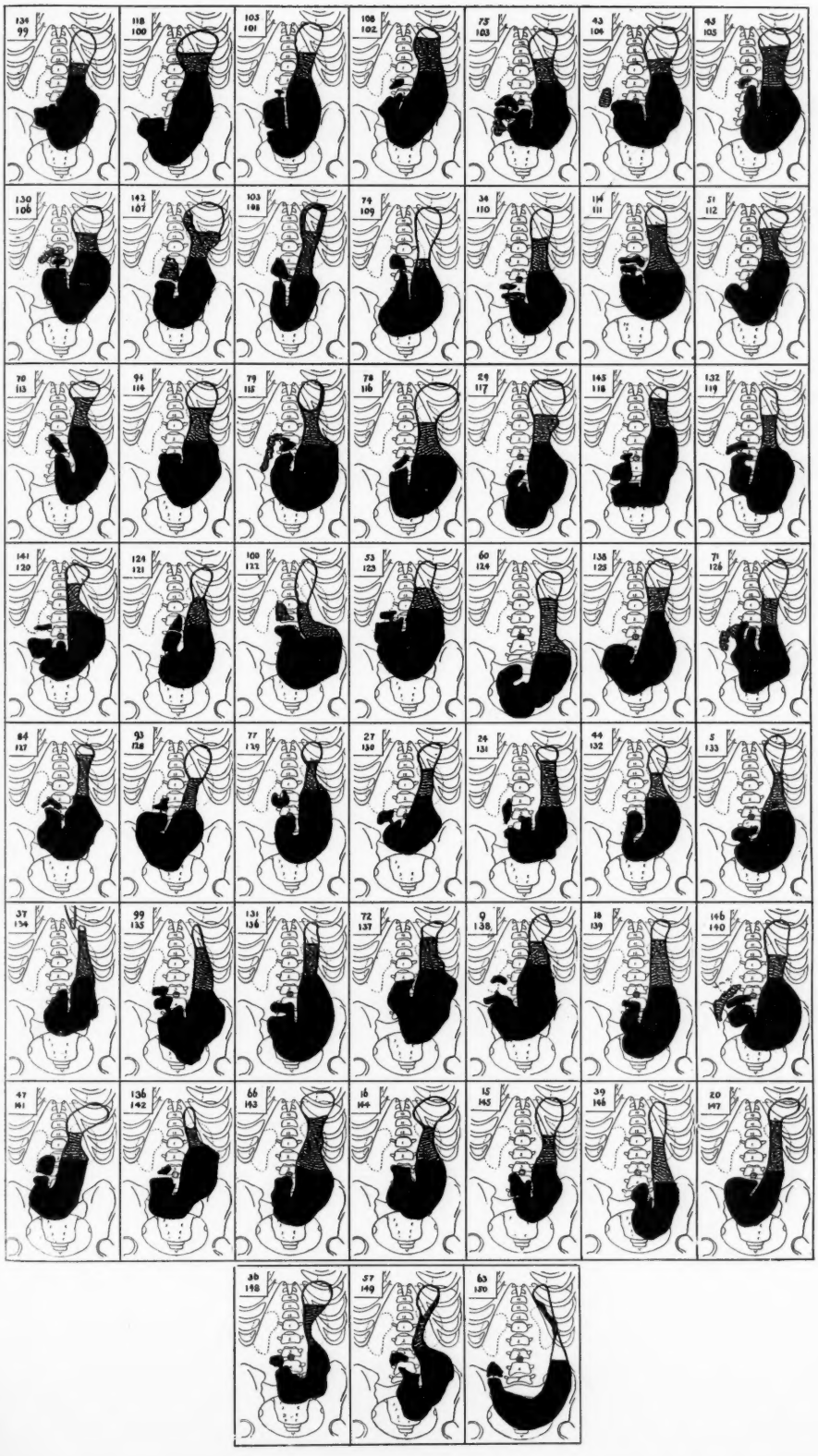
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A. Dropped stomach showing great loss of tone. Note the width of the shadow at the pars angularis as compared with the narrow lumen at the upper level of the barium. The stomach is sagged like a loose bag.

B. The same stomach after five weeks of the treatment described in the text. The lower border is now well above the lower end of the sacro-iliac synchondrosis, and owing to improvement in tone the stomach is now able to maintain a tubular shape from the upper level of the barium down.

THE AETIOLOGY OF RICKETS, EARLY AND LATE

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With Plates 6 and 7

Part I.

Preliminary Statement.

The investigations which have resulted in the writing of this paper came to be made in the following circumstances. On my being posted to the Nasik district of the Bombay Presidency in September, 1920, I began inquiries into the dietary of the poorer classes of the community, the earliest of which was conducted among the constables at the Police Head-quarters and the labourers at the Acetone Factory, and was directed towards the question of the sufficiency of their pay. The results of this inquiry showed that these two classes of men and their families were living on a dietary consisting of an excess of carbohydrate, and very deficient in animal fat and vegetables, and that anaemia and a scorbutic condition were commonly found among them.

The investigation was then extended to the families of the comparatively well-to-do, clerks and others on a monthly pay of Rs. 50 and upwards, who were found to consume a much larger amount of milk and ghee (clarified butter), and whose diet in consequence showed no such fat deficiency as was found among constables and labourers. The omission of milk and ghee from the dietary of the lower classes was admittedly due to the, for them, prohibitive cost of these articles.

While these inquiries were going on, about 2,000 children of all ages up to 12 were examined in Nasik and in the various towns in the district. The majority of these children were the sons and daughters of agriculturists, artisans, and labourers. The results showed that, though most of these children appeared to have a scorbutic taint, very few showed signs of rickets, and in none of the infants was active rickets found. It therefore appeared to be true that rickets was a rare disease in the district: and the first conclusions come to were that the diet of the poorer classes, as a whole, contained an excess of carbohydrate (taken in the form of bajri, a millet) and a deficiency of vegetables and fats,

particularly animal fats; and that these errors in diet accounted for the conditions found.

But meanwhile a few cases of late rickets were brought to the Civil Hospital for treatment, and, as the numbers of such cases and of early rickets began to work up as a result of cures obtained, it became more and more evident that, far from being a rare disease, rickets was a very common complaint in Nasik city; and that its existence had been cloaked, and so had escaped detection, by the fact that it occurred in one class alone, the well-to-do Hindu and Mahomedan families, and that late rickets had not been recognized by the local medical practitioners as rickets, but had been treated as a form of malaria, or rheumatism, under the name of 'haddi tap' or bone fever.

Now at the present time the aetiology of rickets is being discussed from two points of view. The first opinion (Mellanby and Hopkins) is that it is a deficiency disease due to lack of the anti-rachitic vitamin in the dietary, though the holders of this opinion also admit that other factors, such as an excess of carbohydrates, a deficiency of protein, and a want of fresh air and exercise, are supplementary causes.

The contrary opinion (Findlay) is that a lack of fresh air and exercise is the most potent cause of the disease.

It is a commonplace remark in India that the poor live on the verge of famine; and, if the generalization is a true one, this deficient dietary should render the children liable to rickets. But there are other sharp contrasts between the conditions of life among the poor and those to be found in the cases of the well-to-do, and the most prominent of these is the mode of life—especially of the women of the two classes. It has been an immemorial Indian opinion that women should, as far as possible, live a life of seclusion, and modesty is the most prized of virtues in that sex. But, among the poor, seclusion is impracticable, for a wife's help is needed not only in the fields but also with the artisans.

The purdah system has therefore been confined to the upper classes, and is regarded as a mark of social position. A Mahomedan woman, who has not practised it, often goes into purdah as soon as her husband's means will allow of it; all the well-known Mahratta families, such as the Bhonslas of Shivaji's house, have their women 'gosha'; and the members of the theocracy, the Brahmins, though they repudiate the charge that their women observe 'purdah', all readily admit that they are kept secluded by custom, if not by religion.

In this paper, then, I propose first of all to describe at length the habits and customs of the different classes, and follow this with a discussion of results obtained from the diet inquiry. In the second part of the paper, I will consider rickets from the clinical aspect and discuss the aetiology of the same from results obtained; and, lastly, I will mention some points regarding the clinical features and aetiology of late rickets.

Social and Economic Conditions in the Town of Nasik.

The Nasik district covers an area of 8,140 square miles, and is situated at the top of the Western Ghats about 100 miles from Bombay. The district embraces country of very variable character, that to the north and west being hilly and malarious with a heavy rainfall, while to the east it merges into the Deccan plain with a much lighter rainfall and a more salubrious climate. The hilly tracts are inhabited by aboriginal tribes, Bhils, Kolis, and Konkanis, while Mahrattas and other classes of Hindus occupy the plains. The Brahmins and other high-caste Hindus are usually found in the larger towns. Mahomedans are not very numerous.

In Nasik itself the population is sharply divided into two strata:

1. The upper stratum—locally known as the pandarpeshas, or wearers of white clothes—includes pleaders (lawyers), priests, merchants, shopkeepers, and Government clerks. This class would correspond to the upper middle class in England. These families often own the houses which they occupy, and their incomes range from Rs. 50 per mensem upwards. The majority of this class, i.e. practically all the pleaders, priests, and Government clerks, are Brahmins. Nasik is a sacred city and a point of pilgrimage, and on this account the local Brahmins are rigidly orthodox, much more so than in other and non-sacred towns of India. This class also includes the other high-caste Hindus, who trade and keep shops, and well-to-do Mahomedans who are chiefly merchants, contractors, and tradesmen.

2. The lower stratum is composed of artisans, agriculturists, and labourers. It includes the lower Hindu castes, the poorer Mahomedans, and the large class of untouchable Hindus or depressed outcastes—Mahars, sweepers, &c.

It is rather difficult for one used to Western customs to realize how sharply these two classes are differentiated from one another. There is no question of social intercourse between the two, and marriage is strictly confined to caste. In many ways, however, the classes resemble one another, and similar factors operate in both. Their general conditions of life are the same as regards climate, sanitation, early marriage, incidence of malaria, clothing, and so on. It may indeed be said that the two classes resemble each other in every way except two—habits of life and diet—and in these we have an exceedingly sharp contrast.

The extensive inquiry by Miss Ferguson into the social and economic conditions in Glasgow in 1917 (1) brought out clearly the close relationship between fresh air and rickets. The difficulty, however, in her inquiry was the fact that rickets was not found to any appreciable extent in the well-to-do classes, rickets being associated with poverty and overcrowding, i. e. with poor diet and lack of fresh air and exercise. It followed from this that those factors which are at present considered to produce rickets—diet and lack of fresh air—were both found in the same class, and hence, in order to determine which of the two was the causal factor, it became necessary to compare families in the same social class, i. e. those

families that were rachitic with those that were not; and it would therefore hardly be expected that any great difference in diet would be found. The well-to-do classes were necessarily left completely out of the inquiry, and so a valuable control was lost.

In the present inquiry, we find a very different state of affairs. Rickets in Nasik is far more prevalent among the well-to-do, and hence, instead of comparing different sections of the same class with one another, we can compare one complete class with the other, and since one is well-to-do and the other poor, we at once meet with certain strong contrasts as regards food and mode of life, but not in the way that we would expect. We find that while the well-to-do eat the best food, in this class the lack of fresh air and exercise is most marked, while the reverse occurs in the poorer; hence, we have our factors arranged in an extremely suitable manner for the purpose of study. In Glasgow, both the factors were found in the poorer class and neither in the well-to-do; in Nasik one class possesses factor A, but not B, while the other class has factor B, but not A.

Habits of Life.

The individuals of Class 1, for occupational reasons, generally lead a sedentary life. They seldom play games and rarely go for walks. At the same time, they are much more rigidly bound by customs, partly religious and partly social, and these customs are more carefully observed in Nasik than in many other places. These customs cannot be defied without incurring social and, in many cases, religious ostracism, i. e. being outcasted. Here, again, it is difficult for one who has not resided in India to realize the significance of these facts. The customs are particularly binding on the women, and there is little doubt that their strict observance is due almost entirely to the prejudices of the women themselves, who are thus subjected to conditions of life which would never be tolerated in England.

Mahomedan women of Class 1 are all strictly purdah, and even when they travel in a carriage or cart, have to be screened from public view. They practically never leave the house except to visit relatives, and, as a result of this, children are seldom taken out. In any case, a newly-born child is not usually taken out for at least three or four months, and this period is very considerably prolonged if by any chance the child is suffering from a slight cold, malnutrition, or other complaint. Even if the children are healthy, the very nature of the mother's existence prevents their being taken regularly. When they can walk and otherwise look after themselves, they run about like ordinary children. About the age of 12, girls again go into purdah, and from that day till their death they seldom leave the house.

The high-caste Hindu women are not technically purdah. They may go out when they like, but they have to devote a great part of their time to cooking and housekeeping. There is also a tradition of extreme modesty amongst them, and for these reasons a high-caste Hindu woman seldom leaves her house for more

than half an hour daily. They do all the cooking and housework and only go out to attend marriages, to go to the temple, or to perform religious ablutions at the river. The last object is now rarely carried out, as most houses have water laid on from the sacred Godaveri. The women occasionally go on pilgrimages. The following are striking instances of the 'semi-purdah' found in this class:

(*a*) On her husband's death, the widow's head is shaved; she is restricted to wearing one garment only, and to one meal a day; she must not leave her husband's house for a year.

(*b*) A newly-confined woman must not leave her room for three months. During the first month at least the room is carefully closed up so that the woman and child may not catch cold, and during this period she is unclean. On May 28 (the hot season of the year), I saw a Brahmin woman who had been confined six weeks previously. She was in the corner of an inner room, and was surrounded by curtains so that every ray of light was excluded and the entrance of fresh air prevented as far as possible. There was a charcoal brazier burning in this confined space. When the curtain was drawn back, it was with the greatest difficulty that I could see the woman; yet she had lived in this condition for six weeks. This is only an instance of what is almost universal among women of the better classes, but no power of imagination can picture the horror of the scene. The child is, of course, kept with the mother, and so it does not see the light for the first two or three months of its existence.

(*c*) A newly-born child is not taken out of the house as a rule for the first six months of its life. The date of its first walk abroad is delayed till an auspicious day arrives, and in some cases which I have seen this has been when the child was a year old. In several other cases, where the child was supposed to be delicate, this period has been prolonged up to eighteen months and even two years. Even after the child is taken out, it does not get a daily outing; it is taken out only occasionally.

(*d*) A woman must not frequent public places where men are to be met.

Infant marriage prevails, and on reaching the age of 12 a girl who has been attending school is sent to her husband's house, where she does all the cooking and housework under the mother-in-law's directions. In other words, she enters the semi-purdah of the Hindu married woman.

At this point I desire to emphasize the fact that in this stratum of society in Nasik (and I include both Hindu and Mahomedan) there are two periods in the woman's life when she is exposed to the purdah factor—in infancy and after about the age of 12. In the case of men, there is but one period, and that is in infancy. The relationship of early and late rickets to these periods will be shown later.

Housing.

Many of the houses of the well-to-do are ancestral, and they are often large and well built, though not in the same sense as this is understood in England. They are of a different design, the leading idea being privacy for the women.

Since the houses are more crowded together than in England, this privacy can only be obtained by cutting down the window space of those rooms most occupied by the women.

Mahomedans emphasize this idea of privacy, and build as far as possible so that they cannot be overlooked. The windows are small and high up and the rooms are dark, especially the kitchen. The housing conditions of these women are extremely bad. This statement is borne out by Dr. (Miss) Greenfield of Poona, who says, 'When I came to Poona, I was shocked to find Mahomedan women living with no yard or open roof, and purdah seemed more horrible than it had in the North' (2). In England there is no parallel to such conditions.

Hindu houses generally have a large reception room in front on the ground, or first, floor, and the rest of the house is taken up with numerous small rooms behind. The kitchen is among these, and the women and children spend most of their day in these small dark rooms. The darkness of these rooms is intensified by the fact that the walls are discoloured with smoke, and while the women are working the children are laid in the corner of the room. In the older type of house in Nasik, the bad hygienic conditions must be seen to be appreciated. Such houses form the majority of those in Nasik. There is usually a small dark courtyard a few feet square with dark rooms leading off the surrounding verandah. The rooms are so dark that one can with difficulty see into them from the outside. The rooms in which the women and children spend most of their day are in both types of house very dark, and though a certain amount of fresh air gains admission, the rooms, never stuffy, are very warm for one unaccustomed to them. In the cold weather and rainy season, i. e. two-thirds of the year, the rooms are closed as much as possible. The streets in which the well-to-do reside are narrow, and it will be readily understood that very little light can gain admission to a house where the rooms open into a central, badly lighted courtyard.

In the past few months I have examined a very large number of such houses. The condition of affairs is worse than what one finds among the poorest classes at home. To home conditions, darkness is added, and the women do not go out to anything like the same extent that the poor people at home do.

Turning now to the other class—the lower castes composed of artisans, labourers, and agriculturists—we find a very different picture. The life led is of necessity more active, and more in the open. There are no rules as to purdah and no custom of semi-purdah for the women, who have to work as well as the men in the majority of cases, and especially among the agriculturists. Both men and women have a hard life, especially in years of scarcity. The women are obviously stronger and in better condition than those of the better class, among whom there is often a tendency to stoutness. Owing to the outdoor life, the children cannot be left at home. While the mother is working, the child is placed on a shawl under a tree or in some improvised shelter, and is often given a small dose of opium to keep it quiet so that it shall not require any attention.

The houses occupied by these labourers are usually one-roomed ill-built huts

with a hole in the roof for a chimney. Often they live in bamboo or matting shelters. Their mode of living is poor in the extreme, but their houses are the opposite of air-tight and they themselves are in the open all day long.

In the outlying parts of the district, where the aboriginal tribes are found, the mode of life is in striking contrast to that of Class 1 in Nasik. The people are very poor and seldom obtain regular meals. They are a hardy race, keen hunters, living in the open and capable of considerable feats of endurance. Their houses are mere hovels and their dietary is very poor. At Bandardhara, where a large dam is in course of construction, I had the opportunity of examining the mode of life of several types of Indian. Some came from local famine areas owing to failure of crops in part of the district, and others belonged to a criminal tribe. The conditions of life of all were of the poorest description. The large majority were living in the open or under matting shelters. Adults and children lived in the open all day long: their food was of the poorest kind, and hardly any animal food was consumed. Conditions similar to this prevail in many parts of the district, but they differ but little from those found among the lower castes in Nasik.

It is clear then that we have two classes diametrically opposed. In the better class in Nasik, the women and children live under much the same conditions as one finds among the poorer classes at home, while the poorer classes receive plenty of fresh air and exercise. Before taking up the question of diet among these classes, it would be advisable to consider some of the other factors which have been mentioned by Miss Ferguson in her inquiry previously mentioned.

The present inquiry has been greatly simplified, since in all classes breast-feeding is practically universal. In no case have I found artificial foods being used. Lactation is prolonged up to two years, though it is not uncommon to find it at three, or even four, years. Breast-feeding was usually supplemented with other food about the seventh or eighth month; in the well-to-do classes, cow's milk was always given; among the poorer classes, it was seldom used. Rice was usually employed. It is certain, therefore, that the well-to-do infant got better food and more fat-soluble vitamin than the poorer. This will be borne out when the dietaries of the two classes are considered, as it will be shown that the mothers of Class 1 eat much more of the fat-soluble vitamin-containing foods than do the mothers of Class 2.

In the Glasgow inquiry, it was concluded that the health of the mother was probably merely an index of social conditions, and that at most it could only be regarded as a contributory factor in the development of rickets. This conclusion is borne out in the present inquiry. Brahmin women are as a rule well nourished, but phthisis and anaemia are rampant among them, and this is undoubtedly due to the semi-purdah system of living, so that the health of the mother is merely an index of social conditions. The women of the poorer classes, and the children also, are of much finer physique, and the explanation of this has already been given. I can endorse entirely the statement of Noël Paton and

Watson when they say that 'a point of considerable interest demonstrated in our observations is the more rapid growth of the pups kept in the open air' (3).

Miss Ferguson also concludes that the most striking difference between mothers of the rachitic and of the healthy children was one of personality, which expresses itself in the better care bestowed on the children in the non-rachitic families. In Nasik the child of the Brahmin woman is far better looked after than that of the poorer Hindu so far as cleanliness and tidiness are concerned. In Mahomedan families, on the other hand, the children are always very dirty and often suffer from skin diseases. Later on we shall see that rickets is most frequent among the Mahomedans and better-class Hindu, particularly the Brahmin, so that evidently the want of cleanliness and tidiness is not of prime importance in the causation of the disease. It is possible that the 'better care' mentioned by Miss Ferguson includes the taking out of the child, which no mother would omit to do if she had any idea of the necessary care to be bestowed on a child.

Owing to the fact that in Nasik I am comparing the well-to-do class with the poorer class, it is not necessary to deal with all the factors considered by Miss Ferguson in the Glasgow inquiry. Some of these, however, may be referred to briefly.

During the present inquiry, 100 families of the well-to-do and 124 of the poorer classes in Nasik were visited with a view to determining the prevalence of rickets in each. Factors such as early marriages, the influence of heredity, malaria, or venereal disease, sanitation or climate, need not be considered, as they are common to both classes. The following details with regard to still-births, miscarriages, and infant mortality are interesting:

1. Still-births and Miscarriages.

	Total Pregnancies.	Still-births.		Miscarriages.	
		No.	%	No.	%
Class 1 (well-to-do)	499	4	0·8	32	6·4
Class 2 (poor)	558	7	1·2	19	3·4

2. Infant Mortality.

	Average No. of Children Born.	Average Size of Family.	% of Children who are Dead.
Nasik			
Class 1	4·63	3·26	29·5
Class 2	4·30	2·69	37·6
Glasgow (1)			
Marked rickets	5·1	4·18	18
No rickets	3·87	3·33	13·9

These figures will show the appalling mortality which exists among children in Nasik—a town corresponding to a county town at home. I have not got any evidence to show what this mortality is due to, but a mortality of nearly 30 per cent. among the well-to-do children, compared with 18 per cent. among the poorest families of Glasgow, is eloquent testimony to the unhygienic life in this class, and from what I have seen I am in no way surprised. It is

clear, however, that the two classes are very similar as regards pregnancies, still-births, and miscarriages, and therefore these factors may be neglected so far as our present inquiry is concerned.

A Study of the Dietary of Different Classes in the Town of Nasik.

This was carried out on the lines of similar studies in Great Britain, and the method of investigation was that described in the Report upon the Study of the Diet of the Labouring Classes in the City of Glasgow by Miss Lindsay. It is not proposed to publish the results of the present inquiry *in extenso*, but the more salient points are given below.

In all, the dietaries were studied over 152 weekly periods and the families were divided into two groups: (1) Fitters and clerks. Their pay ranged from Rs. 45 to 250 per mensem. The women of this class lived a very secluded life, amounting to purdah. This class corresponds to the Class 1 described in the preceding part of this paper. (2) Labourers at the Government Acetone Factory and police constables on a pay of about Rs. 20 to 25. None of the women in these families kept purdah. The women had to work in order to increase the family earnings. This class does not represent the lowest-paid worker in the district, but it includes most of the Class 2 mentioned previously. They were chosen for the study because they were living together and could be easily controlled.

TABLE I. *Showing the average Consumption of Food among the poorer and better-paid Classes in Nasik during the year* 1920–1.

Class 1—better paid. Class 2—poorer paid.

Particulars.	Class 1.	Class 2.
Number of families	21	131
Adult equivalent of families	3·12	3·09
Energy value of dietary in calories	2970	3680
Percentage of fat calories in total calories	19·3	10·9
Percentage of cereals in dietary	43·9	75·3
Vegetables per adult per day in ounces	4·6	2·8
Food per adult per day in grm.		
1. Animal		
(*a*) Protein	27·1	9·2
(*b*) Fat	34·4	3·0
(*c*) Carbohydrate	10·0	1·0
2. Vegetable		
(*a*) Protein	62·6	97·0
(*b*) Fat	25·1	41·3
(*c*) Carbohydrate	489·0	687·0
3. Total		
(*a*) Protein	89·7	106·2
(*b*) Fat	59·5	44·3
(*c*) Carbohydrate	499·0	688·0

The Indian dietary does not show the endless variety of food-stuffs seen in European dietaries. Similar articles of diet were eaten by both classes, though

the relative amounts of each varied, and accordingly it was possible to compare one class with another and to note the variations which occurred with increase in income. Moreover, such a comparison makes it possible to judge the effect on the dietary of an increase in the size of the family (other things being equal), and also to show what changes occur as the days pass farther and farther from pay day.

The average results are shown in Table I, and with regard to these the following points may be noted: 1. The caloric value of the dietary in Class 2 is higher than in Class 1. 2. The total fat consumed in Class 1 is greater, and this applies especially to animal fat. The percentage of energy from fat also rises. 3. The cereals consumed in Class 2 are much greater than in Class 1. 4. The vegetables in the diet are deficient in both classes, but particularly in Class 2.

It will be seen that there is a great difference between the two classes. There is a sudden rise in the consumption of animal food, and particularly animal fat. The increase in total fat is not proportionate to the increase in animal fat. The former increases from 44·3 grm. to 59·5 grm., while the latter increases from 3·0 grm. to 34·4, an increase of 15·2 grm. compared with one of 31·4. The fat increase, therefore, in passing from the lower-paid to the higher-paid worker is not merely a fat increase; it is an animal fat increase. This indicates a greatly increased consumption of milk and ghee, as is shown in the following:

	Milk in oz.	Ghee in oz.
Class 1	7·65	0·84
Class 2	1·01	0·05

The consumption of fresh vegetables is deficient in both classes. There is a slightly higher consumption in Class 1—4·6 ounces per adult per day compared with 2·8. While no standard exists for the amount of fresh vegetables necessary in the dietary of the Indian labourer, the quantity consumed is far below that consumed by the British worker, and is much less than the allowance of eight ounces of fresh vegetables per day to the convict in Indian jails.

Generally speaking, it will be noticed that the Indian dietary includes more animal food with increase in income and that it approximates more to European standards. It has been shown by Breinl and Young (4) that the metabolism of natives of tropical countries is the same as that of natives of colder climates, and that in the former nature does not have recourse to a special metabolism to regulate body temperature. The energy requirements in each are the same, provided the basal metabolism is the same. In view of this and of the fact that an increase in income leads to an increased consumption of animal food and to a closer approximation to European standards, it would appear that the suitable dietary for the Indian is roughly the same as for the European. This does not imply that the same energy value is required in the Indian's dietary, for it is probable that his basal metabolism is less, but it does imply that the balance should be approximately the same. Apart from basal metabolism, the members of Class 1 lead sedentary lives, and hence their energy requirements are not so great as in Class 2 or as in the European.

There are other facts to support this view. In this country pay is disbursed monthly, and the expenditure on animal food is greater at the beginning of the month than at the end. This, of course, applies to the lower paid only, and amongst them, just before pay-day, the energy value of the dietary may fall to 2,000 calories or less. Cheaper, i. e. more cereal, food is purchased as the days pass from pay-day, thus permitting of a larger number of calories being purchased per anna. From results obtained, shown in Table II, it will be seen that as the size of the family increases the quality of the dietary is adversely affected in that (*a*) the amount spent on food per adult diminishes, (*b*) the caloric value of the dietary diminishes, (*c*) the percentage of energy from fat diminishes. Similar results are obtained if we take averages of the food consumed by families during the first, second, third, and fourth weeks after pay-day. Lastly, there is the work of McCay on the Bengal Jail Dietaries (5), which shows that if the high cereal dietary is eaten, it is not properly absorbed.

TABLE II. *Showing the effect of the size of the Family among Labourers and Police Constables in Nasik on the Amount spent on and Quantity of Food consumed.*

1. Labourers.				
Adult equivalent of family	1·70	2·55	3·44	4·72*
No. of families in group	13	24	19	16
Cost of food per adult per day in annas	4·24	4·27	3·54	3·20
Energy value of dietary per adult per day in calories	3781	3968	3476	3196
Calories purchased per anna	891	929	981	998
Percentage of fat calories in total calories	12·0	10·7	9·8	9·8
2. Police Constables.				
Adult equivalent of family	1·83	2·65	3·33	4·41
No. of families in group	7	23	17	12
Cost of food per adult per day in annas	5·52	4·25	3·52	3·36
Energy value of dietary per adult per day in calories	4574	3919	3254	3483
Calories purchased per anna	828	923	924	1036
Percentage of fat calories in total calories	13·2	12·0	11·2	10·2

* The figures shown in the last column include families over four adults. The families with an adult equivalent of over five are too small in number for an average to be taken, and therefore they have been included with those families whose equivalent is between four and five.

These facts, I consider, show that there is insufficient money to purchase the more expensive animal food, and this has been borne out by subsequent inquiries. I conclude from this that the dietary of the poorer classes is selected from necessity and not from choice. The lower-paid worker must purchase the cheapest form of food to satisfy his hunger, and therefore the high carbohydrate dietary is not due to racial and climatic causes but to economic. If this were not so, the dietaries between the two classes would not have been so widely divergent and nature would have arranged for the complete absorption of a high carbohydrate diet.

The chief articles of the dietary are bajri (millet), husked rice, wheat, pulses, and sweet oil. Animal food consists of milk, ghee (clarified butter), dry

fish, and mutton. Mutton and dry fish are not eaten by Brahmins and certain other castes. The vegetables vary with the season of the year. There is little doubt that the dietary of Class 2 is deficient in fat-soluble vitamin and in anti-scorbutic vitamin, if one can judge from the food consumed. In any case, the content in these substances is obviously far less than obtains in the case of Class 1. There are thousands of poor Indians in Nasik itself who never touch milk and ghee from the beginning of the month to the end, and whose dietary is over 90 per cent. cereal. It cannot be denied that such dietaries are very deficient in fat-soluble vitamin, while the dietaries of the better-paid workers are much better off in this respect.

When the dietaries of the above classes are considered more in detail, the striking differences between the two are more clearly shown. I am conscious of the fact that the number of families among the better paid are small, but my figures have been completely borne out by inquiries which I make from every patient who comes under my care and which I have obtained in my house-to-house visitation. An increase in the number of families would doubtless reduce the margin of error, but the differences are so distinct that the main form of the curves of distribution would be but little altered.

The Energy Value of the Diet.

The energy value of the dietary of Class 1 was on an average 2,970 calories as compared with 3,680 among the poorly paid. In the former 444 calories, or 15 per cent., were derived from animal food, while in the latter 64 calories, or 1·7 per cent., were so obtained. The distribution was as follows:

1. Total Energy in Calories.

	Totals.		Percentages.	
	Class 1.	Class 2.	Class 1.	Class 2.
Under 3000	12	43	57·1	32·8
Over 3000	9	88	42·9	67·2

2. Animal Food Energy in Calories.

Nil	0	21	0·0	16·0
Under 100	1	80	4·3	61·0
Over 100	20	30	95·2	23·0

It will be seen from this that the lower paid tend to eat less at times than the higher paid and more at others, but the overlap in the two classes is considerable so far as total energy is concerned. In the case of animal energy, it will be noted that 16·0 per cent. of the lower paid eat no animal food whatever, and that 95·2 per cent. of the higher paid eat over 100 calories of animal energy as compared with 23·0 per cent. among the lower paid. It must, of course, be remembered from McCay's work that the higher paid, though they eat less total calories per day, probably absorb a much greater percentage of these than the lower paid. Besides, owing to their sedentary lives, their energy requirements are not so high. Even assuming that the energy value of the dietary of the

well-to-do class is low, it has been shown by Noël Paton and Watson that the energy value plays only a subsidiary part in the production of rickets.

Protein. Among the lower paid, an average of 106·2 grm. of protein was consumed per adult per day, and of this 9·2 grm., or 8·6 per cent., were of animal origin. The better paid consumed 89·7 grm., of which 27·1 grm., or 30·2 per cent., were derived from animal sources. The distribution was as follows:

1. Total Protein in Grm.

	Totals.		Percentages.	
	Class 1.	Class 2.	Class 1.	Class 2.
Under 100	14	56	66·6	42·7
Over 100	7	75	33·3	57·3

2. Animal Protein in Grm.

Nil	0	17	0·0	12·9
Under 10	4	63	19·0	48·0
Over 10	17	51	81·0	39·1

Here, again, we have a considerable overlap in the total protein consumed, though the lower paid tend to eat more. With regard to animal protein, 12·9 per cent. of the lower paid eat none whatever, while 39·1 per cent. eat over 10 grm. Of the better paid, 81·0 per cent. eat over 10 grm.

Fat. The average amount of fat consumed by the better paid was 59·5 grm. as against 44·3 by the lower paid. In the former animal fat amounted to 34·4 grm., or 57·8 per cent., while in the latter it was 3·0 grm., or 6·7 per cent. This brings into prominence the much smaller consumption among the lower paid of fat-soluble vitamin.

The distribution was as follows:

1. Total Fat in Grm.

	Totals.		Percentages.	
	Class 1.	Class 2.	Class 1.	Class 2.
Under 40	2	65	9·6	49·9
Over 40	19	66	90·4	50·1

2. Animal Fat in Grm.

Nil	0	16	0·0	12·2
Under 10	2	104	9·6	79·3
Over 10	19	11	90·4	8·5

Here the overlap is not so marked as in the case of protein. The higher paid tend to eat a larger amount of total fat, and in the case of animal fat the difference is most striking, for while 12·2 per cent. of the lower paid eat none whatever, and only 8·5 per cent. eat over 10 grm., 90·4 per cent. of the higher paid eat over 10 grm. per diem. In this inquiry it was found that 1·5 per cent. of the lower paid ate over 20 grm. of animal fat, while 76·1 per cent. of the higher paid ate over the same amount.

Carbohydrate. The lower-paid worker eats a distinctly larger amount of carbohydrate than the higher paid. On an average, the former consumed 688·0 grm. as against 499·0 by the higher paid. Out of these 688·0 grm.,

1 grm., or 0·1 per cent., was of animal origin, while of the 499·0 grm. consumed by the higher paid, 10 grm., or 2·0 per cent., were from animal sources.

The distribution was as follows:

1. Total Carbohydrate in Grm.

	Totals.		Percentages.	
	Class 1.	Class 2.	Class 1.	Class 2.
Under 500	12	22	57·1	16·7
Over 500	9	109	42·9	83·3

2. Animal Carbohydrate in Grm.

Nil	0	82	0·0	62·6
Under 10	11	48	52·3	36·6
Over 10	10	1	47·7	0·8

The difference between the two classes is seen from the fact that, while 47·7 per cent. of the higher paid consume over 10 grm. of animal carbohydrate, only 0·8 per cent. of the lower paid consume over a similar amount.

Commodities in the Diet.

The articles of food consumed by all classes of Indians are very similar, and the following table will show how the consumption of these articles varies in the lower and higher paid classes. In European countries such striking differences do not occur.

TABLE III. *Showing the Consumption per Adult per Day of the Various Food-stuffs among the Lower and Higher Paid Workers in the Town of Nasik.*

Article.	Lower Paid. Grm.		Higher Paid. Grm.	
Milk	23·3		213·3	
Ghee	1·6		23·1	
Mutton	11·7		60·5	
Dry fish	5·5		1·5	
Eggs	—		4·0	
Bajri	603·1		122·9	
Rice	201·1	877·7	250·6	533·9
Wheat	73·5		160·4	
Pulses	49·3		52·1	
Oil	11·8		15·0	
Sugar	17·4		58·8	
Vegetables	92·6		129·5	

In Miss Ferguson's Glasgow inquiry, it is stated that 'while milk was used by all the families, the average allowance "per man" per day was 256 c.c. in the rachitic and 309 c.c. in the healthier families'; and thus 'there is an appreciable difference in the amount of milk consumed by the two groups'. The quantities of the various food-stuffs consumed by the rachitic and non-rachitic groups are very similar, and in the critical Introduction of the M. R. C. to the above Report it is stated that 'in rickety and non-rickety families respectively, though there seems at first sight to be no significant difference, yet on examination it will be noticed that the rickety families do appear to consume more of

those articles of diet which allow rickets to develop and less of those substances preventing rickets; for instance, they are found to eat more flour, potatoes, sugar, and oatmeal, and less milk, meat, butter, fish, eggs, and cheese. It is true that the figures given are not widely different, but it would be hard to deny that the difference might be sufficient to upset a poised balance.'

In the above table we have figures which are widely different, and on the above view the lower-paid worker eats a dietary which should produce rickets. When the consumption of milk and ghee in the Indian community is analysed, very instructive figures are obtained. The higher-paid workers consumed 213·3 grm. of milk per 'adult' per day, while the lower paid consumed 23·3. The higher paid consumed on an average 23·1 grm. of ghee, the lower paid consumed 1·6. The distribution of these substances among the various families gives equally illuminating results, for while all the higher paid took milk daily, 62·6 per cent. of the lower paid took none at all. Regarding ghee, 14·2 per cent. of the higher paid consumed none as against 78·6 per cent. of the lower paid. The distribution was as follows:

1. Milk in Grm.

	Totals.		Percentages.	
	Class 1.	Class 2.	Class 1.	Class 2.
Nil	0	82	0·0	62·6
Under 50	0	25	0·0	19·0
Over 50	21	24	100·0	18·4

2. Ghee in Grm.

Nil	3	103	14·2	78·6
Under 10	1	17	4·7	12·9
Over 10	17	11	81·1	8·5

The number of the higher paid who do not eat ghee is due to the fact that they take extra milk and make their own ghee from this. The above figures become more instructive when it is mentioned that 47·7 per cent. of the higher paid eat over 200 grm. of milk per day and only 2 per cent. of the lower paid, and also that 52 per cent. of the higher paid eat over 20 grm. of ghee as against 1 per cent. of the lower paid. It has been found that 36 per cent. of the well-to-do families keep their own cow or buffalo.

The dietaries of seven rachitic families—three well-to-do Hindu and four well-to-do Mahomedan—were examined in order to show that the dietaries of rachitic families were in no way inferior to the average of the class as a whole. The results are shown in Table IV.

It is clear from this table that the dietary amongst those families where rickets is found is quite as good as the average of the class as a whole, and that rachitic families consume as much milk and ghee as do the others of their class.

TABLE IV. *Dietaries of Rachitic Families.*

1. Hindu.

	1	2	3
Caloric value of dietary	2741	2667	3000
% fat calories in total calories	20·8	19·6	24·3
Vegetables per day in oz.	6·4	5·3	6·9
Milk in grm. per day	138	288	201
Ghee in grm. per day	11	11·5	12·0
Animal protein	5·7	12·6	8·4
„ fat	16·1	22·2	22·5
„ carbohydrate	6·2	14·0	9·4
Vegetable protein	59·0	51·9	65·4
„ fat	45·2	34·1	56·1
„ carbohydrate	456·3	444·3	470·3

2. Mahomedan.

	1	2	3	4	Average for both classes.
Caloric value of dietary	3612	3666	2859	3409	3136
% fat calories in total calories	17·1	23·0	24·8	20·9	21·5
Vegetables per day in oz.	4·5	2·5	6·4	5·1	5·3
Milk in grm. per day	214	266	115	195	202
Ghee in grm. per day	42·9	49·8	48·0	41·5	30·9
Animal protein	30·4	33·1	21·8	23·5	19·3
„ fat	52·0	60·7	53·1	49·6	39·4
„ carbohydrate	9·6	11·7	5·1	8·7	9·2
Vegetable protein	90·8	76·6	67·2	75·2	69·4
„ fat	14·5	30·0	23·3	27·1	32·9
„ carbohydrate	599·4	567·1	430·1	550·3	502·5

Summary of Part I.

In 1918 Noël Paton, Findlay, and Watson (6), in order to settle the aetiology of rickets, attempted a crucial experiment by keeping pups of two litters in the laboratory and feeding them on plenty of whole milk and porridge, and two pups from each of the litters in the country and feeding them on skim milk and oatmeal. The former developed rickets, while the latter did not do so. The remarkable point is that the artificial conditions arranged by these investigators are found naturally present in Nasik.

In the present inquiry, the general conditions of life in the two classes of the community are similar; but they differ on the point of dietary and social habits. The better dietary is used by Class 1—the middle and well-to-do classes—but Class 2, with the poorer dietary, live an out-of-door life as contrasted with the indoor one of Class 1, and have more fresh air, sunlight, and exercise.

The influence of the dietetic factor is considerably reduced, since all the children of both classes that I have examined are breast-fed, and this is prolonged to at least a year. In Class 1 the breast milk is supplemented when necessary with cow's milk; in Class 2 it is supplemented with rice and seldom with milk. Since the mothers of Class 1 eat a dietary containing more fat-soluble vitamin than those of Class 2, it would follow that the children of Class 1 get more fat-soluble vitamin than those of Class 2.

Therefore, this natural Class 1—leading an indoor life and eating a good dietary—is exactly parallel to the pups which were kept in the laboratory and fed on whole milk and porridge, while Class 2—leading the open-air life and eating a poor dietary—corresponds to the pups kept in the country and fed on skim milk and oatmeal. Therefore, we should expect to find similar results as regards the incidence of rickets in the natural conditions in Nasik as were found in the experimental conditions artificially produced at home.

Part II.

Early Rickets.

I have already mentioned in the introduction that in the early stages of my inquiry I examined a large number of children in the smaller towns and larger villages of the district, and that, as a result of this investigation, I concluded that rickets was not a common condition. But later on I found cases of rickets among the children of the well-to-do, and in order to determine its prevalence I carried out a house-to-house inquiry. During this I found a large number of bad cases of rickets which the parents had not considered it necessary to bring to the hospital for treatment. The importance of this fact is that it accounts for the belief that rickets is not a common disease in the Indian districts. In fact, severe cases are seldom seen, partly on this account and also because the normal high mortality among the children of all classes (which must be much exaggerated in the case of the rachitic ones) also helps to mask the condition. I firmly believe that evidence of severe cases of early rickets is seldom got in later childhood or in adult life because few of the children so affected survive childhood.

Prevalence of Rickets.

In considering the prevalence of rickets in the Nasik district, I propose first to take the cases in Nasik city as shown by the house-to-house inquiry, the hospital returns, and an examination of certain school children, and to compare these figures with those given by other parts of the district. I do so because Nasik conditions differ from those in the rural areas. Outside the city the life led is much more in the open air, and the purdah system, as understood in Nasik, is non-existent. At the same time the purdah-keeping Brahmin and Mahomedan communities are mostly to be found in the city, while, with one exception, there are few such families in the other parts.

I saw 224 families in the house-to-house investigation. These have been grouped into: (1) Class 1, which includes the well-to-do Brahmins, high-caste Hindus, and Mahomedans; and (2) Class 2, consisting of the poor, both Hindus and Mahomedans. I had intended to make three groups—(1) well-

to-do Hindus, (2) Mahomedans, and (3) poor Hindus—but as the number of Mahomedan families is admittedly small, I think the above grouping is better. The poor Mahomedan's diet is similar to that of the poor Hindu, but differs from that of the rich Mahomedan, while he resembles the latter in keeping a modified form of purdah.

All the families in Class 1 consume milk and ghee daily, as has been seen already from the diet inquiry; 36 per cent. of them keep a cow or buffalo, and 46 per cent. own the house they live in. The average income was approximately four times that of the families in Class 2, being about Rs. 100 per mensem. In Class 2 about a third of the families took milk, but the quantity per head was only one-tenth of that consumed per head in Class 1. The lower-caste Hindus keep no purdah whatever, and the poor Mahomedans keep a modified form of it.

The results of the inquiry are shown in the following table:

Incidence of Rickets in Nasik Families.

Class.	No. of Families.	No. of Children seen.	Active Rickets.		Healed Rickets.		Total Rickets.	
			Total.	%.	Total.	%.	Total.	%.
Class 1—								
Well-to-do Hindu	85	277	38	13·7	68	24·5	106	38·2
Mahomedan	15	49	5	10·2	9	18·3	14	28·5
Class 2—								
Poorer Mahomedan	24	73	2	2·7	16	21·9	18	24·6*
Hindu	100	260	1	0·3	16	6·1	17	6·4

* The larger proportion of rickets in the poorer Mahomedans is probably to be accounted for by the partial purdah which they practise, their diet being practically the same as that of the poorer Hindus.

The difference between the two classes is very striking. The well-to-do Hindus give 38·2 per cent. of cases, while the lower-caste Hindus give only 6·4. Again, among the well-to-do, 13·7 per cent. were cases of active rickets, while the figure for the poor is only 0·3 per cent. I saw no severe cases of rickets in this class.

Turning now to hospital cases, I saw 590 children in the dispensary. Of these, 89 showed either active or healed rickets. The distribution among the classes and castes was as follows:

	Children seen.	Cases of Rickets.	% Frequency.
Hindus—well-to-do	103	40	38·8
Mahomedans—all classes	97	30	30·9
Hindus—poor	390	19	4·8

Here again we find the same distribution of the disease among the better-class Hindu and Mahomedan children. Lastly, I examined the boys in one of the municipal schools, ranging in age from 4 to 10. The great majority were Brahmins, Thakurs, and Kasars, who form the well-to-do and better educated

class. The untouchable Hindus are excluded from these schools. Three hundred and forty-three boys were seen, and of these 35 showed genu valgum and 1 a deformed chest, a total of 36 or 10·4 per cent.

In one place only in the Nasik district did the results approximate to those in Nasik, and that was in Sinnar, about 18 miles away. Here there is a large Brahmin population. Two hundred and twenty children were seen, with the following results:

	Children seen.	Cases of Rickets.	% Frequency.
Brahmins	131	25	19·0
Other Hindus	89	6	6·7

These results may advantageously be compared with those obtained in other places where the Brahmin population was practically negligible and where no purdah was maintained.

	Children seen.	Cases of Rickets.	% Frequency.
Chandor—a decayed old town	100	6	6·0
Peint—jungle village	60	1	1·6
Malegaon—industrial town	653	31	4·7
Yeola—trading town	581	29	4·9
Bandardhara—construction camp	172	4	2·5

Taking the district as a whole, we find that out of 1,073 children, whose parents are well-to-do and whose mothers observed purdah, there were 268 cases of active or healed rickets, i. e. 24·9 per cent., while among 2,305 children of lower-caste Hindus there were 113 cases, i. e. 4·8 per cent.

In this inquiry certain interesting facts came to light, and it is necessary to consider these briefly, since I am of opinion that there is evidence to show that the prevailing complaint among the poorer classes is scorbutic in character. The following remarks are based on the examination of 1,947 children from birth to 12 years of age. The majority of these were the children of agriculturists, artisans, and labourers, and included practically all the lower castes of Hindus found in the district.

The two most striking signs met with were pyorrhoea and beading of the ribs. Carious teeth were very uncommon, and in no case did I find the mouthful of carious teeth so often seen at home. Pyorrhoea occurred with great frequency, being found in its various stages in 71·5 per cent. of the children. It begins to appear almost with the eruption of the milk teeth, and at the age of 10 the gums usually showed distinct pyorrhoea and bleeding of the gums readily occurred on pressure. In 90 adults whom I examined, pyorrhoea was present in 72, or 80 per cent., yet carious teeth were uncommon.

Beading of the ribs occurred in 68·7 per cent. of the children seen, and this at all ages up to adult life. On account of its frequency, it was never used as a diagnostic sign of rickets. The beading was not as a rule marked, but was clearly visible as a distinct rosary if the subject was made to bend backwards and so stretch the skin of the chest. I have seen the beading in adults. The worst cases I have seen were in those atrophic children so often found in the

lower classes of Indians. In these there were no signs of rickets. I am of opinion that this sign is probably scorbutic in nature, for the following reasons: (1) Its occurrence at all ages of childhood. (2) The rarity with which rachitic changes accompany beading, and especially in those atrophic children where beading is most marked. (3) The presence of swollen gums, which bleed easily, and the wide prevalence of pyorrhoea in all classes and at all ages. (4) The low consumption of vegetables among all classes. This, we have seen, averaged about 4½ oz. per head. These signs are also common in the well-to-do classes in whom rickets is common.

Another sign requiring notice is the facial or Chvostek's phenomenon. This sign is associated with tetany, a disease closely related to rickets. The phenomenon occurs very frequently, and, curiously enough, I have not found it in children under four years of age. After that age, as will be seen from the following table, its incidence increases with age up to adult life. In old persons its frequency diminishes.

Age.	Children seen.	F.P. positive.	% positive.
1	40	0	0·0
2	46	0	0·0
3	32	0	0·0
4	50	0	0·0
5	85	12	14·1
6	148	33	22·2
7	204	72	35·2
8	210	83	39·5
9	164	77	46·9
10	176	88	50·0
11	129	63	48·8
12	59	32	54·2
Adults	90	53	58·8

The significance of this occurrence with increase in age I have not yet been able to determine, though it is possibly associated with gastric dilatation. I have very frequently come across cases, in adults especially, in which there is enlargement of the liver with tenderness and with constipation, dyspepsia, and dilatation of the stomach. It is also of interest to note that no cases occur below the age of four, when breast-feeding is almost universal. I have no means of testing the electrical excitability in these cases, but I am endeavouring to isolate methyl guanidin from the urine. I may, however, mention that I have met with several cases of adult tetany which showed typical carpopedal spasm and Trousseau's sign. For the present, it is important to note that this phenomenon is not found at the ages when active rickets occurs, and it is therefore very probable that it bears no relationship to this disease so far as Nasik is concerned.

To sum up, I may state that in the Nasik district rickets is a common complaint among the well-to-do Hindus and among Mahomedans, while among the poorer Hindus of the lower castes the disease is comparatively rare. Among all classes, the frequency of pyorrhoea with beading of the ribs suggests that a scorbutic condition is widely prevalent.

Clinical Notes.

It is not my intention to describe in detail the clinical signs of rickets in this district, as the photographs (Plate 6) taken will show that these do not differ from rickets at home so far as bony changes are concerned. There are, however, certain minor differences which I have observed. In Nasik the anterior fontanelle appears to close more quickly than in England. The widely patent fontanelle was not observed so frequently.

Epiphyseal enlargement was the most common sign of the disease in its active stage; it nearly always was well marked and usually affected the wrists only. I never saw a severe case of active rickets in a poor child, and in this class epiphyseal enlargement was almost completely absent. When present, it was very slight. If this enlargement were scorbutic, the reverse incidence should have been found, since the very poorest seldom ate any green vegetables at all.

As has been mentioned above, beading of the ribs was never used as a diagnostic point of rickets owing to the frequency with which it was met. In rachitic children it was just as prominent a sign as at home. The posterior rosary was observed several times in bad cases.

The teeth, even in the most marked rachitic cases, were nearly always in excellent condition. I have mentioned already that in all classes of the population the teeth were in good condition, but that pyorrhoea was very prevalent. In only six cases have I noted that there was a large number of carious teeth.

One point which I would like to mention here is that the infants of the poorer classes are far superior in physique to those of the better classes. Both are breast-fed, and the poorer mothers, though they do not get anything like the dietary of the more well-to-do women, are obviously harder and of better colour. This observation agrees with those of Noël Paton, Findlay, and Watson, who found that the 'country pups' on poorer food thrived much better than the well-fed laboratory animals.

Discussion and Conclusions regarding the Aetiology of Rickets.

The object of this investigation was to test the two opposed hypotheses as to the predisposing cause of rickets. It is held by one school that rickets is the result of a deficiency of fat-soluble vitamin in the dietary, and by another school that it is due to insufficient air, light, and exercise.

It has been found that in Nasik the population is made up of two strata: (1) Class 1, an upper stratum composed of well-to-do Hindus, chiefly Brahmins, and Mahomedans; this stratum forms the educated and moneyed class; and (2) Class 2, a lower stratum of artisans, agriculturists, and labourers who are uneducated and poor.

When these two classes are compared, it is found that in many ways they

resemble one another. The general conditions of life, such as climate, clothing, sanitation, early marriages, &c., are the same in both, and such special factors as pregnancies, miscarriages, and still-births are very similar. In fact, the two classes resemble one another in every way except in personal habits and in diet. Here the two classes are strongly contrasted.

The individuals of Class 1 lead a sedentary life, and they are rigidly bound by customs which are particularly binding on the women. The Mahomedan women of Class 1 are all strictly purdah, while in Class 2 a modified purdah is carried out. Among the better-class Hindus, purdah is also maintained by the women. The effect of this on the children has already been pointed out, and as a result they also are confined to the house till they are able to walk and look after themselves.

The houses of these people are unhygienic to a degree. Stuffiness, as generally understood in England, is not found, but the rooms are extremely dark and the air is often hot. The women and children inhabit such dark rooms all day, and when a woman is confined she is shut up in almost complete darkness for a period of three months in the case of Hindus, and of forty days in the case of Mahomedans. Even after this the child is kept almost continually in a dark house.

When we come to examine the personal habits of Class 2, we find that the artisans and labourers from necessity lead a very active life and a more open one. There are no rules as to purdah, and no custom of semi-purdah for the women, who have to work as well as the men. The children are necessarily kept with their mothers all day, and so they spend all their time during the day in the open. The houses are usually ill-built and far from air-tight.

Turning now to the diet, we again find conditions widely divergent. The diet of both classes has been adversely affected by world prices, a local failure of crops in 1920–1, and high local prices owing to this being the year of a very big pilgrimage to Nasik. The general tendency has been to eliminate as far as possible the higher priced items, such as milk, ghee, vegetables, and meat, and to rely on the cheaper and more filling cereals. In Class 1 the result has been a smaller expenditure on such articles, in Class 2 their practical exclusion from the diet.

All Brahmins (the bulk of Class 1) are vegetarians, but take animal fat in the form of milk and ghee (clarified butter). The average consumption found by experiment was 34·4 grm. of animal fat per day per adult. All families took milk, and 36 per cent. had their own cow or buffalo. When necessary, breast-feeding was supplemented with cow's milk.

The remaining members of this class use a similar diet: but some castes eat mutton, and Mahomedans also eat beef.

In Class 2 mutton may generally be eaten, or in the case of Mahomedans, beef: but neither is procurable on an income under Rs. 30 per mensem. The staple food consists of unleavened millet cakes helped down with condiments and a small quantity of vegetables. The average animal fat consumption was 3·0 grm.

per adult per day. No cows or buffaloes were kept, and when necessary to supplement breast-feeding rice was given. In 62·6 per cent. of the families milk was not consumed at all and in 78·6 per cent. no ghee was eaten.

The dietaries of the two classes differ on the following points: (1) The caloric value of the dietary in Class 2 is greater than in Class 1. (2) The total fat in Class 1 is greater than in Class 2, the animal fat consumed averaging 34·4 grm. per adult in Class 1 as against 3·0 grm. only per adult in Class 2. (3) Class 1 consumes on an average 7·65 ounces of milk per adult per day, and 0·84 ounces of ghee; while Class 2 only uses an average amount of 1·01 ounces of milk and 0·05 ounce of ghee. (4) All families in Class 1 use milk; 62·6 per cent. of families in Class 2 use none.

It follows from these statistics that, even though both classes may consume an insufficient quantity of fat-soluble vitamin, Class 1 obtains very much more than does Class 2.

To sum up, we have in Nasik two classes in the community who resemble one another in every way except as regards dietary and social habits. The better diet is used by Class 1, the middle and well-to-do classes; but Class 2, with the poorer dietary, live an out-of-door life as contrasted with the indoor one of Class 1, and have far more air, light, and exercise.

Turning to the incidence of rickets in these classes, we find that the disease is most common in the families of Brahmins and other well-to-do Hindus, all in Class 1; less so, but still marked, in the case of Mahomedans, who fall partly into Class 1 and partly into Class 2; and slightly in the cases of the 'other Hindus', who all fall into Class 2.

We can now consider the two prevailing hypotheses regarding rickets in the light of these investigations. If a deficiency of fat-soluble vitamin from the diet is the real cause of rickets it should show the four recognized marks of a cause, that is:

1. Rickets should follow where the dietary is deficient in fat-soluble vitamin such as occurs in Class 2; but this class shows the smallest incidence.

2. Rickets should follow immediately on the coming into operation of this cause—the coming of a famine in the district, such as that now prevailing—and should affect those most affected by the famine. At the Bandardhara construction dam I examined 172 children, most of whom were the children of agriculturists from famine areas, and I found only four slight cases of genu valgum. Many of the children were under a year old. Though the dietary of the parents was in most cases destitute of animal food, these infants were plump and well nourished.

3. The incidence should not be affected by other causes, such as sedentary or active habits of life; but rickets is common in the sedentary class and rare in the active one.

4. Rickets should affect those who eat a poor diet, but it does not.

These considerations show that a deficiency of vitamin in the diet cannot be a whole or a principal cause for the prevalence of rickets, for none of the necessary attributes of a cause are present.

But testing the rival theory by the same logical canons we get a positive result.

1. Rickets does follow on a sedentary life and prevails largely in the classes which have adopted a 'purdah' or similar system for their women and children.

2. It follows immediately on the coming into operation of such a cause, for it afflicts those children who are confined to the house after birth and also those who on account of a supposed delicacy have been confined to the house more than their brothers and sisters.

3. Provided this element of seclusion indoors is present, the incidence is not affected by other conditions, such as a more generous diet, better clothing, &c., among the well-to-do.

4. Results show that the incidence of rickets is very heavy where such conditions of an indoor life are found.

5. All cases of rickets so far treated, ten in number, have yielded to a course of fresh air and exercise, showing that removal of the cause removes the effect. All other factors remained constant and no medicine was given. In all cases improvement was very rapid.

The evidence which has been put forward in this paper strongly supports the views of Dr. Leonard Findlay regarding the aetiology of early rickets, which are already well known. The difficulties which this investigator had in establishing his hypothesis were undoubtedly due to the impossibility of obtaining suitable conditions in Glasgow for the purposes of inquiry. From a knowledge of Findlay's work, I was at once able to appreciate the importance of local conditions in Nasik, and hence my present paper must be looked upon as an extension of the work already done by Findlay in 1915 and subsequent years.

The facts therefore show that if the lack of fresh air, light, and exercise is taken to be the cause of rickets, it is found to result where such a cause exists. This test therefore gives a positive logical result.

Late Rickets.

Late rickets, or 'rachitis tarda', is a disease which is found as late as the twentieth year of life in individuals who were previously healthy and non-rachitic. Such a definition, therefore, does not include cases of relapsed rickets, though it is probable that the aetiology in both is the same. Findlay (1) states that primary cases of late rickets after the age of four are undoubtedly rare. He also states that 'symptomatically and anatomically this variety (late rickets) of the disease is not different from that occurring during infancy, except that, since the growth of the cranial bones is not so active at this period of life, changes in the skull are slight or absent. On account of the absence of a negative balance in the calcium metabolism in examples of late rickets, Schabad considers that it is aetiologically different from that variety occurring in infancy. Pain and difficulty in walking, epiphyseal enlargement, rosary, bending of bones, flaccidity of muscles are all present and may be extreme.'

I have been able to collect seventeen cases in Nasik, and it has been possible to study them from the aetiological standpoint and from the point of view of treatment. Owing to the comparative rarity of such cases, I propose first of all to make a few clinical notes on some of them.

Case 27. Hindu Brahmin, female, aged 14. States that she was quite healthy up to the age of 12, and that she had no deformities before her present illness. Married at 12, but not residing with her husband. Before that age, ran about like other children and went to school, but at 12 she was confined to the house and hardly ever went out. Shortly after this, she began to suffer from pain in the knee-joints and waist, and this was accompanied by a low fever (bone fever) which lasted some months. The condition got steadily worse, and when seen she had great difficulty in walking. The gait was waddling and genu varum was present. There was slight lordosis. Facial phenomenon marked. Slight but distinct beading of the ribs present and also epiphyseal enlargement of the wrists.

The dietary in this case has been good and contained 288·2 grm. of milk and 11·5 grm. of ghee per day. The parents are high-caste Brahmins. X-ray photo showed typical late rickets.

Treatment very successful. Has lost all pain and can walk 2 or 3 miles without difficulty.

Case 293. Hindu Brahmin, female, 16½ years. Complains of difficulty of walking and pains in the left thigh and hip of two years' duration. Up till three years ago patient went about like other children, but at that time she got married and went to live with her husband. Since then, she has seldom left the house, especially during the past two years, owing to the presence of pain in her limbs.

She states that two years ago she got an attack of bone fever which lasted for six months. This fever was of a low type and was accompanied by pains in the waist and thighs. It was followed by an attack of dysentery which lasted three months. She then began to have difficulty in walking, and this condition has got progressively worse.

At present she walks with a waddling gait. Genu valgum is present and is distinct: it is definitely stated that this appeared after the commencement of the illness. Epiphyseal enlargement of the wrists is marked, and both wrist and ankle joints are tender on pressure. Beading of the ribs is present, and the costochondral junctions are very tender. Lordosis is also present, and there is tenderness on pressure over the pelvis and back. F.P. very marked. Patient very well nourished.

Menses appeared eighteen months ago. No children. Diet has always been good, and she eats plenty of ghee and milk. A cow is kept. Her house, like the one in the previous case, is in old Nasik and is very unhygienic.

X-ray photo showed typical late rickets. Treatment very successful. Pains gone, and can now walk long distances.

Case 298. Hindu Brahmin, female, 13 years. Complains of pains in the hips and knees while walking: duration, five months.

Married a year ago, but not yet living with her husband. Before marriage was going to school and running about like other children: at that time had no deformities of any kind. For the past year she has been practically always confined to the house. Her walking about is nothing to what it was a year ago.

Five months ago, she began to suffer from pain in both buttocks, and this spread down to the knees. She also had pain in the ankles on walking. No history of fever or diarrhoea.

At present marked epiphyseal enlargement of the wrists and ankles (see

Plate) and slight genu valgum of the right knee. Patient is thin and spare. Distinct beading of the ribs, but no tenderness. F.P. marked, involving all the muscles of the face.

Milk and ghee consumed daily in the house. Her father is not very well off, but for the past year the patient has spent her day in the father-in-law's house, where a buffalo is kept, and as a result she has had plenty of milk every day.

X-ray photo shown (Plate 7). Treatment with fresh air very successful. No pain. Can walk long distances.

Case 299. Sister of above, 11 years. Inability to walk and deformity of the limbs of two years' duration.

Up to the age of 9 years was running about like other children and had no deformities whatever. Two years ago child began to have difficulty in walking. No history of fever or diarrhoea. With difficulty in walking, had pains in the lumbar region. This was followed by swelling of the wrists and ankles and later by deformities of the tibiae. Same diet as in above case. She was not in purdah when the condition started two years ago, but since then she has not been out of the house.

At present, there is marked outward bending of the tibiae at the lower ends. Very distinct enlargement of the wrists and ankles. Pigeon chest. Beading of ribs present. F.P. positive. If patient lifted, severe carpopedal spasm appears. Trousseau's sign easily elicited. Cannot walk or extend legs.

Since open-air treatment six weeks ago, all signs of tetany have disappeared. She can now walk the length of the ward by herself.

Case 402. Hindu Marwari, female, 17 years. Difficulty in walking of 2½ months' duration. Married eleven months ago, and since then has been much more purdah than she ever was before. Up till 2½ months ago was quite healthy. She states that for the past five or six months she has had 'bone fever' accompanied by pain in the back. There were no bony deformities before the present illness. She has no children.

At present, genu valgum marked. Epiphyseal enlargement of the wrists slight. Beading and tenderness of the costochondral junctions. F.P. negative. Lordosis present. Has great difficulty in rising up if she has sat down for a few minutes, and when she has risen she cannot walk for two or three minutes. No treatment followed.

Case 17. Hindu Brahmin, female, 13 years. Difficulty in walking and pains on walking of one year's duration. Illness started a year ago with fever, which lasted four or five days. With this, difficulty in walking started, and also pains in the pelvis and thighs, and these have remained the same till now.

Patient unmarried. Still attending school, but after she returned from school she stayed in the house all the time. At present, genu valgum distinct, and this has appeared in the past year. No epiphyseal enlargement. F.P. positive and very distinct. History of carpopedal spasm. Trousseau's sign present.

Patient well nourished and fat. Diet good, as patient belongs to a well-to-do family. Tetany appeared with fever a year ago and again during the second attack of fever which she had ten days ago. No treatment followed.

Case 88. Hindu Brahmin, female, 13 years. Complains of pains in the limbs and cough of four months' duration. Healthy up to four months ago, and at that time she began to have trouble in walking, and day by day since then the trouble has got worse. Now she cannot walk any distance.

Patient went to school till two years ago, and then she was confined to the house. The family is well off, and milk and ghee are consumed daily. For the past fifteen days has had fever in the evenings, but no pains. Beading present with tenderness of the costochondral junctions. Epiphyseal enlargement of

the wrists with tenderness. No deformities. F.P. positive. Looks fairly well nourished. No treatment.

These clinical histories are typical of the majority of cases seen, and with regard to the seventeen cases which I have examined the following points require notice:

1. All the cases were found in females.

2. Sixteen cases were found in Brahmins and well-to-do Hindus and in Mahomedans, i.e. in those classes who keep purdah or semi-purdah and whose dietaries were good. One of the cases was found in a Tanner, a caste which does not usually keep purdah, but in this particular case it was admitted that the woman rarely left the house. One case only was found among lower-class women, though I saw many more of such women than I did of Brahmins.

3. In practically all the cases, it was definitely stated that milk and ghee were consumed daily, and frequently a cow was kept. The worst cases were found among poor Brahmins who had to keep semi-purdah, but whose diet was not as good as that of the well-to-do.

4. The mean age of incidence of the condition was 15·6 years. The maximum was 32 years and the minimum 9 years. The majority of cases began between 12 and 13 years.

5. The majority of cases showed deformities of the lower limbs, but it would appear that the later the onset the less likely are the limbs to be affected and the more likely the pelvis.

In late rickets, then, we have a condition resembling clinically early rickets, and which from the aetiological point of view presents the following features:

1. It occurs in the well-to-do and not in the poorer classes. The former we have seen obtain a much larger supply of fat-soluble vitamin.

2. It occurs where the purdah or semi-purdah life is adopted, i.e. in the Brahmin, well-to-do Hindu, and Mahomedan.

3. It occurs soon after the purdah life is adopted, and this change of life is not accompanied by any change in diet. It does not occur in the poorer classes or in men, who do not adopt the purdah life. As already stated, early rickets and late rickets both occur after the purdah life is adopted, i.e. in infancy and about the age of 12. In the former, both sexes are affected because both are confined to the house; in the latter, only females, because they only maintain purdah about the age of 12.

4. Its occurrence is not affected by diet, i.e. if diet be a cause, the incidence of late rickets should not be affected by purdah, but it is. If purdah is a cause, it should not be affected by diet: and it is not, because we find the disease where the diet is best and do not find it where the diet is worst.

5. It does not occur in the poor who eat a diet poor in fat-soluble vitamin, but who take plenty of fresh air.

The same conclusion is therefore arrived at as in the case of early rickets, viz. late rickets is the result of the purdah and semi-purdah modes of life. This

is confirmed by the result of treatment. Other things being equal, removal of the cause removes the effect. In six cases of late rickets treated on open-air lines, all the patients lost their pains very rapidly and were able to walk much longer distances than they could before. In no case was medicine prescribed, and the diet taken was brought from the patient's house, and was exactly what she had always been having.

General Conclusions.

From the inquiry in this district, I have seen many cases of rickets, both early and late. These conditions occur almost exclusively among well-to-do Hindus and Mahomedans. The purdah form of life leads to a lack of fresh air, sunlight, and exercise. The dietary of this class has been shown by investigation to be far superior to that of the poorer class in which these diseases are almost completely absent. The larger consumption of milk and ghee entails a greater supply of fat-soluble vitamin to the class which suffers most from these diseases. It has already been shown that, by the logical canon of difference, a deficiency of fat-soluble vitamin cannot be the principal cause of rickets.

This investigation, then, bears out entirely the crucial experiment devised by Noël Paton, Findlay, and Watson. The natural conditions of life in Nasik are exactly parallel to the experimental conditions arranged by these observers, and from the incidence of rickets in Nasik exactly similar results have been obtained. The conclusion is therefore come to that the most important aetiological factor in the production of rickets is lack of fresh air, sunlight, and exercise.

I desire to thank Mr. S. J. Shah, my assistant in the hospital, for his invaluable help in obtaining cases. I would also thank Mr. A. Appleyard, M.Sc., and Mr. F. Hirst, A.R.C.S., of the Government Acetone Factory, for carrying out my chemical analyses and for much helpful criticism; Colonel T. S. Novis, I.M.S., of Bombay, for allowing me to have the X-ray photographs done in the J. J. Hospital in Bombay; and finally, Mr. S. J. Murphy, I.C.S., District Judge of Nasik, for his valuable assistance in arranging about my house-to-house inquiry, and in helping to overcome the prejudices of the people.

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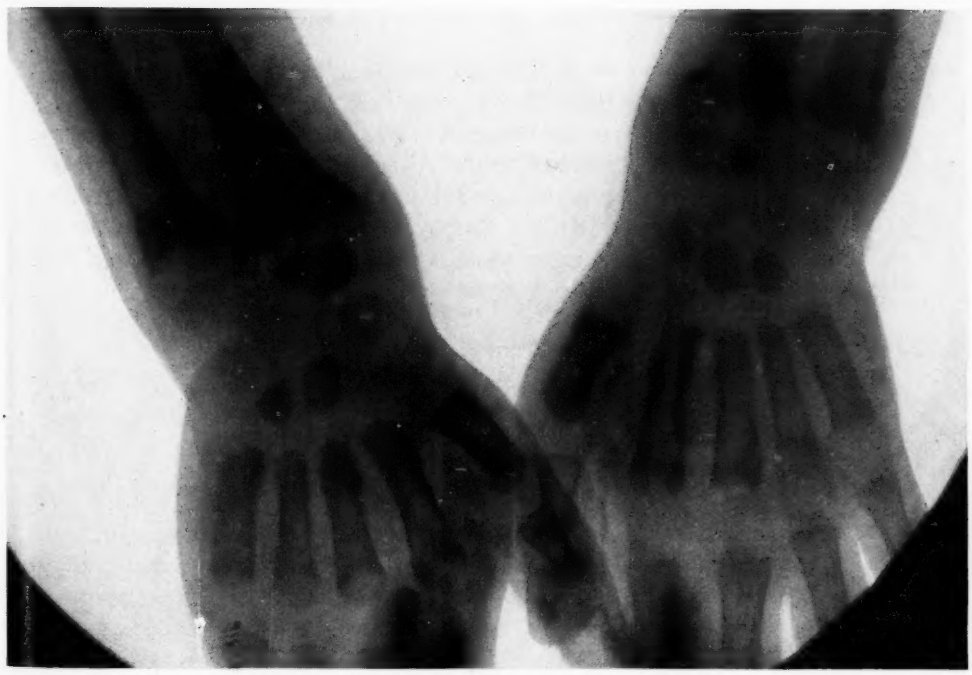
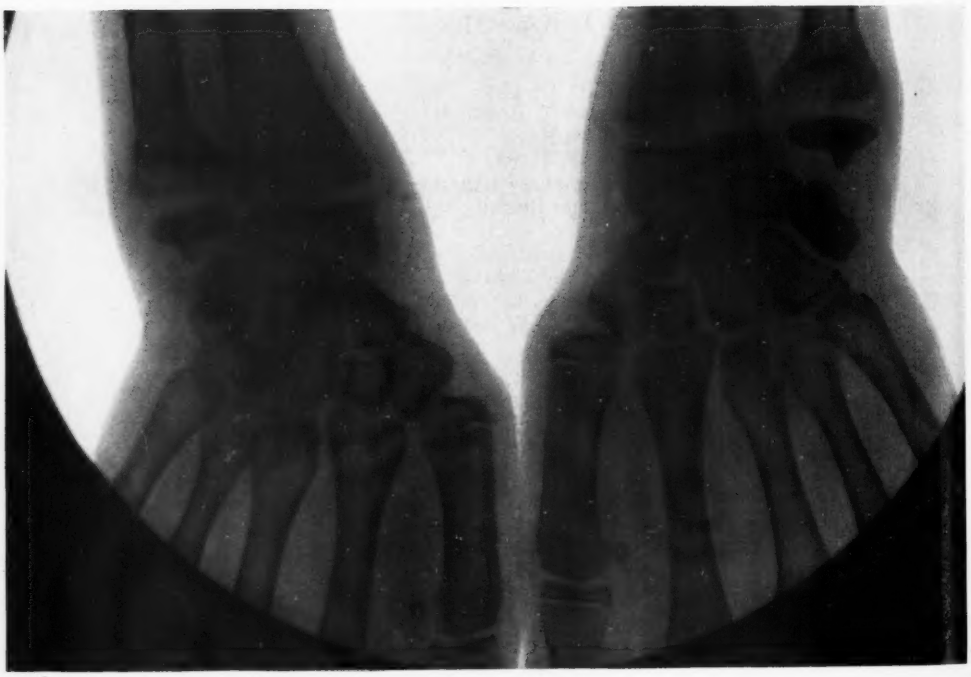
Normal Wrist



Rickets. Brahmin Child

Mahomedan



Brahmin. Case 298

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

FOURTEENTH ANNUAL GENERAL MEETING

THE FOURTEENTH ANNUAL GENERAL MEETING was held at Birmingham on Friday and Saturday, May 13 and 14, 1921, at 10 a.m. The sessions were held in the University Buildings, Edmund Street.

The President, Dr. Judson Bury, was in the chair.

The Minutes of the last General Meeting, having been published in this Journal, were taken as read and confirmed.

Election of President. Dr. Kauffmann was elected President for 1921–2.

Honorary Member. Dr. Judson Bury, the retiring President, was elected an honorary member of the Association.

The election of Officers, members of the Executive Committee, and new members took place in accordance with the lists given below.

Treasurer: Sir William Hale-White.

Secretary: Dr. H. Morley Fletcher.

Members for England:

Dr. J. R. Charles.
Professor T. R. Elliott.
Dr. John Hay.
Dr. A. F. Hurst.
Sir Humphrey Rolleston, K.C.B.
Dr. James Russell.

Members for Scotland:

Dr. Francis Boyd.
Professor G. L. Gulland.
Professor T. K. Monro.

Members for Ireland:

Dr. J. E. MacIlwaine.
Dr. Gilman Moorhead.
Dr. Francis C. Purser.

New Members.

Adolphe ABRAHAMS, O.B.E., M.D., 24 Park Crescent, W. 1. Phys. Royal Chest Hospital, Assist. Phys. Westminster Hospital.

Lawrence BALL, M.B., 53 Newhall St., Birmingham. Phys. to Out-patients and Pathologist Queen's Hospital, Birmingham.

Cecil CLARKE, M.D., 3 The Fosseway, Clifton, Bristol. Assist. Phys. Bristol General Hospital.

ASSOCIATION OF PHYSICIANS

A. Geoffrey Evans, M.D., 37 Queen Anne St., London, W. 1. Assist. Phys. and Assist. Director of Med. Prof. Clinic, St. Bart.'s Hospital.

J. F. Gaskell, M.D., The Uplands, Great Shelford, nr. Cambridge. Assist. Phys. Addenbrooke's Hospital, Cambridge.

John Henderson, M.D., 6 Newton Place, Glasgow. Phys. Royal Infirmary and Prof. of Med., St. Munro's College, Glasgow.

William Johnson, M.D., 26 Rodney St., Liverpool. Assist. Phys. Royal Southern Hospital, Liverpool.

Hugh Maclean, M.D., D.Sc., St. Thomas's Hospital, London, S.E. 1. Director of Med. Clinic and Consulting Bio-Chemist, St. Thomas's Hospital.

Geoffrey Marshall, C.B.E., M.D., 31 Wimpole St., London, W. 1. Assist. Phys. Guy's Hospital.

J. Campbell Meakins, M.D., 12 Oxford Terrace, Edinburgh. Christison Prof. of Therapeutics, University of Edinburgh.

A. I. Simey, M.D., St. John's, Horton Crescent, Rugby. Phys. Hosp. of St. Cross, Rugby, Med. Officer Rugby School.

E. F. Skinner, M.B., 342 Glossop Rd., Sheffield. Assist. Phys. and Phys. for Skin Diseases, Sheffield Royal Infirmary.

J. Douglas Stanley, M.D., 21 Broad St., Birmingham. Phys. to Queen's Hospital, Birmingham.

W. W. D. Thomson, M.D., B.Sc., 25 University Square, Belfast. Assist. Phys. Royal Victoria Hospital, Belfast.

W. H. Willcox, C.B., C.M.G., M.D., 40 Welbeck St., London, W. 1. Phys. to St. Mary's Hospital, Con. Phys. to H.M. Home Office.

S. A. Kinnier Wilson, M.D., 14 Harley St., London, W. 1.

A vote of thanks to Dr. Judson Bury, the retiring President, was proposed by Sir William Hale-White and seconded by Dr. Kauffmann, the President-elect.

The Treasurer then presented his report showing a balance of £280 10*s.* 10*d.* The report was adopted.

The President then called on Sir Archibald Garrod, who invited the Association to meet at Oxford in 1922. The invitation was unanimously accepted.

Dr. Tyson had given notice of motion 'that in future the meetings be held on Thursday and Friday instead of on Friday and Saturday'. Dr. Tyson having agreed to the addition of the words 'if possible', the motion was carried nem. con.

The Secretary read a letter from Dr. Gibson, Secretary to the Editors of this Journal, notifying the Association that Professor T. R. Elliott had been elected as Editor in the place of the late Sir William Osler.

The Secretary read a letter from Lady Osler thanking the Association for the messages of sympathy sent to her at the last Annual Meeting.

A letter was read from Dr. Gulland inviting the Association to meet in Edinburgh in 1923.

SCIENTIFIC BUSINESS

FRIDAY, May 13, 10 a.m. MORNING SESSION

1. Dr. Judson Bury on *The Significance of Some Early Symptoms of Nervous Diseases* referred chiefly to pain, numbness, motor disability, and the plantar reflex. He gave instances, in some cases of serious disease, of the long duration of subjective symptoms before the appearance of objective signs. He criticized the view that many of the early symptoms of disseminated sclerosis were due to hysteria, and considered that the rapid oscillation of the symptoms, especially of the reflexes, was best explained by an intermittent evolution of the toxins of the disease.

Dr. Hurst drew attention to the importance of testing the vibratory sense, as loss of this sensation is often one of the earliest signs in nervous disease, particularly in tabes.

Dr. Stanley Barnes also spoke.

2. Professor E. Mellanby (introduced) described the experimental work he had been carrying on to investigate the results of feeding animals on various kinds of fat. It was found that animals fed on fats, other than cod-liver oil, developed marked hyperplastic changes in the thyroid gland, resembling those characteristic of Graves's disease. He was at present engaged in investigating the influence of fats in the dietary of a series of cases of Graves's disease.

Sir William Hale-White asked if the sex of the animals employed in these experiments had been noted.

Sir Archibald Garrod, Drs. Spriggs, Hutchison, and Fraser also discussed the communication.

3. Professor A. J. Hall related the case of a miner of 25 who had repeated and severe attacks of haematemesis, and was regarded as a case of splenic anaemia. Splenectomy was proposed, but was postponed until his condition had improved, and was not performed. Two or three months later ascites developed and was treated by frequent tappings. A very loud venous hum was present at the lower end of the sternum. Ultimately the ascites disappeared and the patient gradually improved and was now in good condition. The Wassermann blood reaction was negative. The venous hum had persisted. Professor Hall asked for suggestions as to the diagnosis, and this was discussed by Drs. Poulton, McKendrick, Barnes, and Campbell.

4. Dr. Gordon Holmes related a case of tumour of the suprarenal cortex in a young woman. Her development was normal till the age of 19. Then menstruation ceased suddenly, and the secondary sexual characteristics underwent very marked changes—atrophy of the mammae, and appearance of coarse hair on the lips, chin, and body. Her configuration became essentially male. The clitoris enlarged and the uterus was very small. Sugar tolerance was considerably raised. A tumour was felt in the right side of the abdomen which gradually increased in size. It was removed, and was found to be encapsulated with a structure microscopically resembling normal suprarenal tissue. The patient menstruated 26 days after its removal, for the first time for some years, and the male characteristics rapidly disappeared. She now appeared to be quite normal. Photographs were shown illustrating her appearance before and after the removal of the tumour.

Sir A. Garrod, Drs. Hurst and Fletcher discussed the communication.

2–3 p.m.

A remarkably fine collection of clinical cases was shown at the University in the students' reading-room, which had been most kindly lent for the occasion.

FRIDAY AFTERNOON. 3 p.m.

1. Dr. J. W. Russell showed charts recording the amount of albumin passed in a case of orthostatic albuminuria. Variations were discovered, especially in relation to diuresis; certain diurnal and nocturnal variations were suggested, and a remarkable development in the albuminuria taking place in the course of a year was recorded.

Dr. Glynn related a case of functional albuminuria which persisted throughout life.

Dr. Symes pointed out the importance of estimation of the renal efficiency in cases of functional albuminuria.

Drs. Bury, Thursfield, Barnes, and Sir William Hale-White and Sir A. Garrod joined in the discussion.

2. Professor F. R. Fraser recorded the results obtained by the application to clinical investigation of the Dale and Evans method for determining the reaction of the blood. It was found that greater variations occurred in disease than had been suspected.

Dr. Poulton commented on the results obtained.

3. Dr. A. P. Thomson (introduced)—Observations on Blood-Sugar in Diabetes. The rate of fall of the blood-sugar varies during the 'starvation' period. When the rate of fall is slow the results of treatment as a rule are not satisfactory. He related a case of pancreatitis in which after operation the blood-sugar fell to normal.

Drs. Spriggs, Ryle, and Thomson criticized his remarks.

4. Dr. A. B. Soltau described the rhythmic changes in the systolic blood-pressure. Variations occur about five times per minute and affect both the systolic and diastolic pressures. They are probably due to a central cause.

The Annual Dinner was held at 7 for 7.30 at the Queen's Hotel. The President, Dr. Kauffmann, was in the chair and 64 members and guests were present.

The official guests were Sir Gilbert Barling, Bart., Vice-Chancellor, and C. Grant Robertson, M.A., C.V.O., Principal of the University of Birmingham.

SATURDAY, May 14, 10 a.m.

Before the scientific business began Dr. R. Hutchison, with the consent of the President, proposed that one session at the next Annual Meeting should be devoted to a general discussion on one subject and that suggestions as to subjects should be sent to the Executive Committee. The proposal was seconded, but the motion was lost by 17 to 14 votes.

1. Professor T. R. Elliott recorded a case of pericardial effusion caused by a bronchial cyst. The patient, a young man, was admitted to Hospital with a large pericardial effusion which was tapped on three occasions. The fluid removed contained altered blood and, on one occasion, cells which suggested the diagnosis of endothelioma of the pericardium. He left the Hospital in an improved condition, but was again admitted with a large pericardial effusion. Two and a half pints of fluid were removed. This was followed by pneumo-pericardium and great collapse. X-ray examination showed a large spherical mass at the base of the heart to the left of the sternum, which rapidly increased in size. Mr. Gask operated and succeeded in almost completely removing the tumour. The operation was followed by recovery. The tumour was regarded as an aberrant growth from the bronchi.

2. Dr. Ball related two cases of subacute atrophy of the liver—one in a female of 34, the other in a child, which he regarded as dependent on a vascular lesion of the liver. The liver in both cases exhibited obliterative endophlebitis and consequent hepatic insufficiency. Ascites was a prominent feature in both.

Dr. H. Campbell suggested that the phlebitis was due to a toxin of hepatic origin.

3. Dr. A. F. Hurst gave a communication on gastric diathesis. He recognized that there was a definite tendency to duodenal ulcer which he classed as a duodenal diathesis. A family history of duodenal ulcer was quite common, and he gave examples of this. If a large number of normal persons were examined by X-rays it would be found in a considerable proportion that the stomach was small and showed hypertonus with rapid emptying, and was situated higher than normal. He urged the importance of advising such persons to adopt prophylactic measures. With regard to achylia, he pointed out that this was found in all cases of pernicious anaemia, and in at least 70 per cent. of achylic patients indigestion was present. He suggested that if some septic conditions occurred in an achylic individual pernicious anaemia might develop.

Dr. R. Hutchison referred to the difficulty of explaining the great preponderance of duodenal ulcer in the male. He considered the hyperchlorhydria was the cause of the hypertonic state of the stomach.

Dr. French suggested examination of the relatives of pernicious anaemia patients to ascertain if achylia were present.

Dr. Kauffmann suggested that excessive smoking might account for the greater prevalence of duodenal ulcer in men than women.

Drs. Ryle, Spriggs, and Charles joined in the discussion.

Dr. Hurst in reply pointed out that the rapid emptying of the stomach was the danger in duodenal ulcer. He stated that achylia was present in most patients after gastro-enterostomy.

4. Dr. Ryle gave the results of investigations in cases of gastric hyposecretion and achylia. He was of opinion that these conditions could be clearly recognized only by the fractional method. As to the type of case in which he had found hyposecretion—6 had gastric ulcer; 6 complained of epigastric pain and flatulence, and most of these had undergone appendicectomy; 3 had visceroptosis; 2 had gall-stones: all cases of acne rosacea (female). The treatment he advised was careful dieting with dry meals, regular exercise, and the administration of HCl.

Dr. Spriggs advocated the old test-meal method in private practice rather than the fractional method.

Dr. Hurst advised one-drachm doses of dilute HCl in a tumblerful of lemonade or albumin water.

Drs. Hutchison, French, Marsh, Campbell, Carey Coombs, and Sir William Hale-White also spoke.

Owing to the coal strike and the great difficulty in travelling experienced by the members it was agreed to prolong the morning session and not to hold an afternoon meeting.

Dr. Hume was unable to give his communication as he was unfortunately absent through illness.

5. Dr. Poulton discussed the types of dyspnoea occurring in diabetes, uraemia, chronic lung disease, and chronic heart disease. In the first two of these conditions the dyspnoea was due to the presence of acid bodies in the blood: in the two last to the presence of CO_2 in the blood.

6. Dr. Herbert French related a case of dermato-myositis in a boy of 16 which in the early stages suggested a diagnosis of trichinosis owing to the presence of muscular pains and difficulty in speaking and swallowing, though there was no eosinophilia. There was considerable pyrexia. The skin showed marked inflammatory changes and haemolytic streptococci were found in its deeper layers. The patient ultimately made a complete recovery.

Dr. Nixon and Dr. Thursfield spoke on the subject.

From 2 to 3 p.m. another large collection of interesting clinical cases was shown in the reading-room of the University.

A special demonstration was given by Dr. Hurst to show the results of treatment on certain cases of Deaf Mutism by Suggestion. The cases selected were those presenting a normal vestibular reaction, and these Dr. Hurst was gradually training to listen and to hear sounds and spoken words. The results obtained were most interesting and remarkable.

THE REACTION OF THE BLOOD IN RELATION TO DYSPNOEA

By FRANCIS R. FRASER, J. P. ROSS, and N. B DREYER

(From the Medical Professional Clinic, St. Bartholomew's Hospital)

In 1920 Dale and Lovatt Evans (1) described a method for the colorimetric determination of the reaction of the blood by dialysis. Their method is an improvement on that described by Levy, Rowntree, and Marriott (2), in avoiding errors due to the loss of CO_2 from the blood and from the dialysate, and is a modification of that described by Scott (3). With this method it appeared that the reaction of human blood could be simply determined by the application of arterial puncture, introduced by Hürter (4) in 1912 and utilized by Stadie (5) and others. The method has many advantages over those in which the hydrogen electrode is used and those depending on the oxygen dissociation curve in the rapidity and ease with which the determinations are made. It has been pointed out by Lovatt Evans (6) that the colorimetric method gives values of P_H that are 0·2 higher than those obtained by the hydrogen electrode, but that, apart from this, the two methods are in agreement. He has pointed out that this is due to a constant error in the determination by the hydrogen electrode method.

By the method of Dale and Lovatt Evans, the blood is run into a collodion sac tied to a vulcanite holder and the full sac is then corked. The sac holds about 3·0 c.c., and stands in a cylindrical glass vessel surrounded by 1·0 c.c. of 0·85 per cent. sodium chloride in freshly distilled water which fills the vessel, over which the vulcanite holder fits tightly. After standing for fifteen minutes, the dialysate is covered with liquid paraffin and compared with phosphate solutions of known P_H, using neutral red as the indicator. The solution of known P_H is obtained by titration in the comparator in an exactly similar vessel until the same tint is obtained as in the dialysate. In this titration three-standard phosphate solutions of $P_H = 6·5$, $7·5$, and $10·5$ are used, and starting with 1·0 c.c. of solution $P_H = 7·5$ one or other of the two solutions is run in drop by drop from a fine pipette until the colours are identical. From prepared curves the P_H of the final mixture can then be read. We have determined the reaction of arterial blood in (*a*) eleven normal male adults, and the reaction of the venous blood in addition in five of them, and the reactions of both arterial and venous blood in (*b*) nine patients with signs of severe circulatory failure, and in (*c*) seven with signs of severe renal disease.

Method.

To obtain human arterial blood, blood is withdrawn from the radial artery at the wrist into an all-glass syringe containing sufficient liquid paraffin to coat the walls and obliterate the dead space. A pinch of powdered carbonate-free potassium oxalate is added to the paraffin in the syringe. The blood is then run directly into the collodion cell of the dialyser with no more exposure of the blood to the air than in the original method. The dialysing chambers are ready beside the bed, and the blood run into them immediately it is obtained. The determinations of the P^H are then made as in the method of Dale and Lovatt Evans.

Because of the high values of the P_H obtained in normal subjects precautions were taken that no change in reaction should result from the glass or other apparatus used. The glass was given prolonged treatment with strong hydrochloric acid and repeated washings, and the liquid paraffin in the syringe prevents any possible change from contact with the sides.

The venous blood is obtained by withdrawing it from one of the superficial veins in front of the elbow without constriction. In some cases constriction had to be used before the needle could be inserted, in which cases no blood was withdrawn until the constriction was released and all signs of congestion had disappeared. In the patients this method was modified to allow of comparable readings in the same patient on successive occasions during the progress of his condition, by taking the venous blood with the arm in a water bath at 100° F. The arm is put in the bath at a temperature a few degrees higher, and when it has cooled to 100° F. it is withdrawn sufficiently to allow of the venous puncture. In this way a constant temperature condition for the periphery of the limb is obtained.

Results.

(*a*) Normal. Determinations of the reaction of normal human blood were made on eleven healthy male students, and the results are recorded in Table I and Chart I.

TABLE I.

Case.	Date.	P_H. Arterial.	P_H. Venous.
1	13.10.20	7·68	
	27.10.20	7·67	
	3.11.20		7·71
2	20.10.20	7·68	
	3.11.20		7·71
	10.12.20		7·69
3	26.10.20	7·67	
4	27.10.20	7·65	
5	29.10.20	7·70	
6	6.11.20	7·72	
7	9.11.20	7·64	
8	10.11.20	7·66	
9	12.11.20	7·69	
10	17.11.20	7·68	7·71
11	7.12.20	7·67	7·64

Healthy male adults aged 20–40.

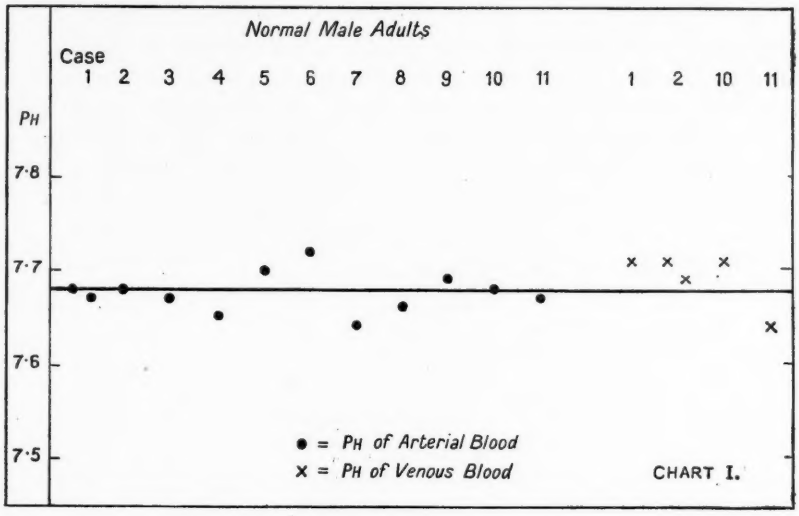


CHART I.

It will be seen that the values for P_H so obtained all fall about 7·68, the highest being 7·72 and the lowest 7·64. The authors of the method maintain that it is accurate to 0·03, so that our findings point to a very constant value for the reaction of the blood in healthy young adults and to the reaction of the venous blood being practically identical with that of the arterial blood. The value 7·68 is 0·3 higher than the value found by the hydrogen electrode method, and the calculations of Lovatt Evans only account for a difference of 0·2. The reason for the further difference of 0·1 is still obscure, but the constancy in the eleven cases makes it justifiable in regarding 7·68 as the normal value for the method.

(*b*) Severe heart failure with valvular disease. Determinations were made in seven cases with severe heart failure due to valvular disease of the rheumatic type. All had some degree of cyanosis and all had orthopnoea. It is extremely difficult to gauge the degree of dyspnoea present, as some of the cases showed no distress when at rest in bed in the sitting or reclining posture, but all showed distress on the slightest exertion or even on speaking. In any question concerning the reaction of the blood the presence of respiratory distress at the moment when the blood is withdrawn is of importance, and therefore a note as to the degree of respiratory distress present at the time, in addition to the orthopnoea, has been included in the tables. Oedema was present to some degree in all seven cases, and in two (Cases 14 and 16) it was pronounced, with marked signs of oedema of the lungs at the bases posteriorly. Varying amounts of albumin in the urine were present at times in all the cases, and in some casts were found, but in none was it considered that the condition of the urine was indicative of lesions other than those due to the circulatory insufficiency and congestion. Three of the cases (Cases 12, 13, 14) came to autopsy, and a fourth died shortly after leaving the hospital.

In two cases of aneurysm of the thoracic aorta, determinations of the reaction of the blood were also made. In both the clinical picture was that of heart failure with aortic regurgitation. Case 19 had Cheyne Stokes's respiration, and Case 20 had orthopnoea and evidence of more severe damage to the kidney functions than could be accounted for by the circulatory derangement.

The values obtained in these nine cases are shown in Table II and Chart II.

TABLE II.

Case.	Age.	Date.	Lesion.	Dyspnoea.	P_H. Arterial.	P_H. Venous.	Result.
12	23	8.12.20	Aortic and mitral regurgitation. Auricular fibrillation	Slight	7·76	7·75	Died 21.1.21
13	14	15.12.20	Aortic regurgitation. Mitral stenosis. Auricular fibrillation	Severe	7·74	7·78	
		19.1.21	—	Less	7·81	7·68	Died 2.3.21
14	67	12.1.21	Aortic and mitral regurgitation	Very severe	7·78	7·77	Died 18.3.21
15	26	4.2.21	Mitral stenosis	Severe	7·73	7·68	Died 7.21
16	39	26.1.21	Mitral stenosis. Auricular fibrillation	Very severe	7·76	7·75	
		9.2.21	—	Less	7·95	7·88	
		2.3.21	—	Less	7·80	7·75	
		25.3.21	—	Slight	7·74	7·65	Discharged improved 30.4.21
17	41	9.3.21	Mitral stenosis	Severe	7·83	7·80	
		20.4.21	—	Less	7·83	7·73	Discharged improved 1.5.21
18	45	4.5.21	Mitral stenosis. Auricular fibrillation	Slight	7·81	7·62	Discharged improved 25.5.21
19	56	21.4.21	Aneurysm of thoracic aorta. Aortic regurgitation	Cheyne-Stokes	7·76	7·73	Discharged not improved 18·7.21
20	45	9.9.21	Aneurysm of thoracic aorta. Aortic regurgitation	Slight	7·76	7·69	

Cases of severe heart failure with valvular disease. All had orthopnoea except Case 19, and in column headed 'Dyspnoea' is indicated the degree of additional respiratory distress present at the time the blood was withdrawn.

These results indicate that in severe heart failure the reaction of the blood is more alkaline than in health. The degree of alkalaemia does not appear to have a close relationship to the severity of the clinical condition, and cases with severe respiratory distress and those with little or no distress alike have a blood reaction that is more alkaline than in health. Case 16 is of peculiar interest in that four determinations were made, and that on the second occasion a reaction of $P_H = 7·95$

was obtained, the farthest to the alkaline side in the whole series. Between the first and second determinations digitalis had been administered and the ventricular rate had fallen considerably, with a lessening of the respiratory distress and much improvement in the patient's general condition, but without any diuresis or diminution in the ascites and oedema. Before the third determination, diuresis had begun, and the fourth determination was made shortly before the patient's discharge, and at a time when she was able to walk about the ward.

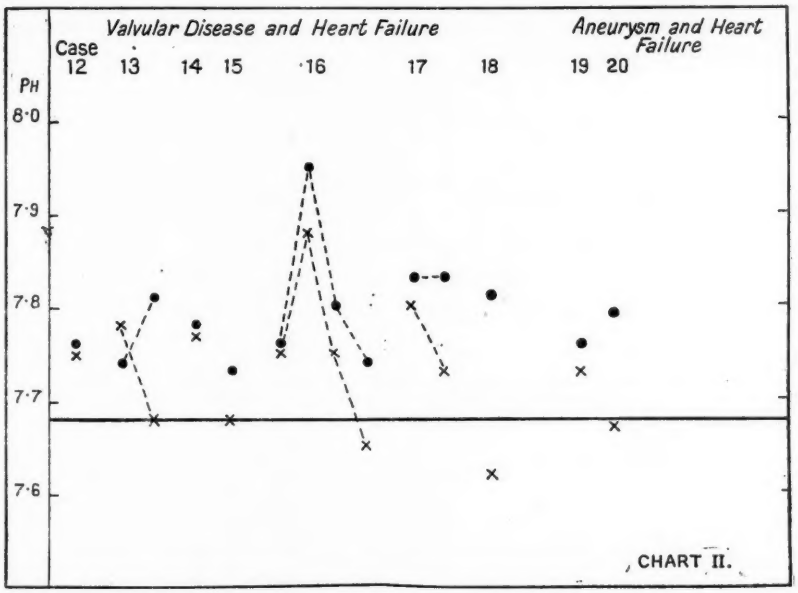


CHART II.

The reaction of the venous blood was in general close to that of the arterial and usually slightly more acid.

(*c*) Severe disturbance of kidney function. The cases of severe kidney disease fall into three groups. Cases 21 and 22 had orthopnoea and severe dyspnoea, with acute bronchitis and oedema that was renal in distribution. Both had albuminuria and casts, while Case 21 had apparently an acute recurrence of a chronic diffuse nephritis of recent origin. Case 22 had a chronic diffuse nephritis, with high blood-pressure, retinal haemorrhages, and headache. In both there was a moderate urea retention and both recovered well.

Cases 23, 24, and 25 presented the clinical picture of severe uraemia and had high degrees of urea retention. Cases 23 and 25 ended fatally in hospital, and Case 24 discharged herself and died at home. Case 23 showed slight 'grouped' breathing, but otherwise none of them showed dyspnoea or other respiratory disturbance at the time of the puncture.

Cases 26 and 27 had haematuria and acute nephritis. Case 27 showed a typical clinical picture of infective endocarditis, which was confirmed a few days later by autopsy, and had an increasing urea retention. Orthopnoea and consider-

able dyspnoea were present. In Case 26 there was evidence of severe disease of the aortic and mitral valves, with fever and enlarged spleen. A high degree of urea retention developed, with signs of severe uraemia, from which he recovered. Pyaemic abscesses developed later, and the patient left hospital and died at home, so that the original diagnosis of infective endocarditis has not been confirmed. Moderate orthopnoea and dyspnoea were present.

The reactions of the blood in the cases of this group are recorded in Table III and Chart III.

The figures for the blood urea were obtained by Dr. George Graham by Ambard's hypobromite method.

TABLE III.

Case.	Age.	Date.	Diagnosis.	Blood Urea mg. per 100 c.c.	Dyspnoea.	P_H. Arterial.	P_H. Venous.	Result.
21	27	26.11.20	Acute bronchitis and acute and chronic nephritis	73	Very severe	7·59	7·36	
		5.1.21	—	—	Slight	7·64	7·61	Recovered
22	55	1.12·20	Acute bronchitis and chronic nephritis	140	Severe	7·67	7·53	
		17.12.20	—	—	Slight	7·65	7·67	Recovered
23	25	30.5.21	Acute uraemia	270	Grouped slight hyperpnoea	7·36	7·38	Died 3.6.21
24	33	27.6.21	Uraemia	180	Absent	7·42	7·38	Died
25	27	14.3.21	Acute uraemia. Anaemia	320	Absent	7·72	7·69	Died 14.3.21
26	47	16.2.21	Infective endocarditis, pyaemia, uraemia	300	Moderate	7·70	7·73	Died 10.21
27	28	5.5.21	Infective endocarditis, diphtheria, acute and chronic nephritis	140	Severe	7·73	7·60	Died 22.5.21

Cases with symptoms of severe renal inadequacy. Cases 21, 22, 26, 27 had orthopnoea and the additional respiratory distress at the time the blood was withdrawn that is indicated in the table.

That a condition of acidaemia should be found in cases of severe renal disease is in keeping with the results of much previous work by other methods. That severe acidaemia should be present without dyspnoea, as in Cases 23 and 24, is therefore the more noteworthy, even if slightly increased ventilation unrecognized clinically were present. Case 25 had been receiving large quantities of alkali both intravenously and by the mouth, and the absence of acidaemia and of hyperpnoea in this instance may be accounted for in this way. Cases 26 and 27, although showing severe renal symptoms and urea retention, were clinically cases

of heart failure, and the alkalaemia found in them may be in spite of, rather than because of, the disturbance of renal function. Case 26 was receiving large quantities of alkali by the mouth, but Case 27 was not. In Cases 21 and 22 the reaction of the venous blood was considerably more acid than the arterial when the dyspnoea was severe, but on recovery the venous was approximately the same as the arterial.

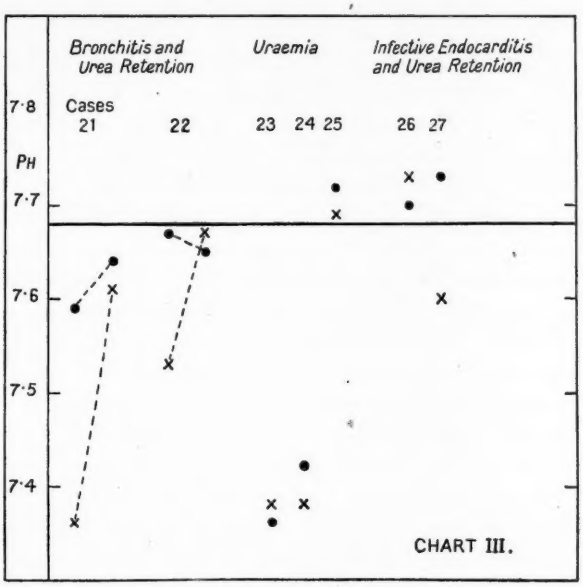


CHART III.

Discussion.

Further work is in progress to endeavour to determine the mechanism of the abnormal reactions of the blood here described, and particularly of the alkalaemia seen in the cases of heart failure. It is only proposed here to state the reactions obtained and the type of case in which the different reactions were found. Any hypotheses as to the mechanisms involved and the essential disturbances of function are therefore out of place.

Lewis, Barcroft, and others (7), (8) investigated the reaction of the blood in cases of dyspnoea by means of the power of absorbing oxygen, and came to the conclusion that the dyspnoea, often paroxysmal, seen in elderly patients with arterio-sclerosis, headache, and frequently renal symptoms was accompanied by an acidaemia, while dyspnoea in the purely cardiac cases, especially in young people, was not. Our results are substantially in agreement with theirs, but point also to the cardiac dyspnoea being accompanied by an actual alkalaemia.

The reactions in the cases of severe uraemia are of much interest as indicating the possibility of severe acidaemia without respiratory distress or hyperpnoea that could be recognized clinically, and the wide difference between the reactions

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of the arterial and venous bloods in the two cases of nephritis with acute bronchitis shows the possible effect of increased ventilation in altering the reaction of blood.

The most alkaline reaction for arterial blood found was $P_H = 7{\cdot}95$ and most acid $P_H = 7{\cdot}37$, and it is of importance to note that life is compatible with such variations from the normal $P_H = 7{\cdot}68$.

It must be recognized that there is no method of gauging the extent of hyperpnoea clinically, especially in patients who are seriously ill, and that such terms as orthopnoea, dyspnoea, and air hunger are terms describing clinical appearances that cover a wide range of respiratory distress and give no indication of true pulmonary ventilation. For this reason cases with well-pronounced characteristics have been selected for investigation. Whatever the immediate mechanism of the altered reactions may prove to be, it is obvious that respiratory distress in diseased persons cannot be simply explained in terms of hydrogen-ion concentration of the circulating blood. Nor was there a quantitative relation between cyanosis and respiratory distress in the cases of heart failure. Campbell and Poulton (9) have shown that in cases of cardiac dyspnoea there is a high CO_2 tension in the arterial blood, and suggest that this may be a factor in the causation of the dyspnoea, but their work has not been confirmed.

That the activity of the respiratory centre must depend on the chemical condition at the centre and not of the arterial blood is obvious, and it is possible that in diseased persons the state of the circulating blood is not a true indication of the conditions at the centre. It seems probable that the centre may be affected in a great variety of ways, and that our knowledge of dyspnoea in diseased persons cannot be materially advanced until we take into consideration not only the complicated conditions of the circulating blood, but also the condition of the respiratory centre and the pathological changes that may occur in it, independent of oxygen supply, carbon dioxide tension, and hydrogen-ion concentration.

Conclusions.

1. The colorimetric method for determining the reaction of the blood by dialysis can be simply applied to clinical investigation by means of arterial puncture.

2. The average reaction of the blood in healthy young adults by this method is $P_H = 7{\cdot}68$, and the limits in health are from $P_H = 7{\cdot}72$ to $P^H = 7{\cdot}64$.

3. The reaction of the venous blood is in health approximately the same as that of the arterial blood.

4. In cases of heart failure with valvular disease the reaction is more alkaline than normal.

5. Dyspnoea is found associated with alkalaemia as well as with acidaemia.

6. Pronounced acidaemia may be present without dyspnoea.

7. Reactions of arterial blood as alkaline as $P_H = 7{\cdot}95$ and as acid as $P_H = 7{\cdot}37$ are compatible with life.

Description of Cases.

Case 12. Male, aged 23 years. History of rheumatic fever at 17 years, and since then able for light work only.

Admitted 28.10.20, after one month of palpitations and shortness of breath. Pale, orthopnoeic, dyspnoeic, enlarged liver, râles at bases of lungs, heart enlarged, signs of aortic regurgitation, mitral stenosis, and regurgitation. Auricular fibrillation. Ventricular rate 178. Radial pulse 102. No oedema of legs. Respirations 34.

8.12.20. Much improved. Pulse 76, no deficit. Respirations 24. Orthopnoea, dyspnoea on slightest exertion. Felt faint during arterial puncture, and vomited.

20.1.21. Died. Diagnosis confirmed.

Case 13. Male, aged 14 years. History of repeated attacks of acute rheumatism and shortness of breath, cough and swelling of the ankles for nine months.

Admitted 13.12.20. Cyanosed, orthopnoeic, dyspnoeic, persistent cough, enlarged liver, slight oedema of ankles, heart greatly enlarged and signs of aortic regurgitation, and mitral stenosis and regurgitation. Auricular fibrillation. Ventricular rate 120. Radial pulse 86. Respirations 28.

19.1.21. Slight improvement. Pulse 70, no deficit. Respirations 20. Dyspnoea less. Rheumatic nodules.

2.3.21. Died. Diagnosis confirmed.

Case 14. Female, aged 68 years. History of rheumatic fever at 9 years and 42 years, and of 'heart trouble' since. Shortness of breath, swelling, and pain in abdomen, and swelling of legs for two months.

Admitted 6.1.21. Extremely cyanosed, orthopnoeic, and dyspnoeic, oedema of legs and back, ascites, enlarged liver, râles all over lungs, and fluid in both pleural cavities, heart enlarged, sounds masked by râles. Temperature 97° F. Pulse 120. Respirations 40. Blood-pressure 130–60. Urine: albumin—a trace; a few granular casts.

18.1.21. Died. Autopsy: cardiac hypertrophy and dilatation, old and recent endocarditis of aortic and mitral valves, and some recent mural vegetations on the auricular wall. Cirrhosis of liver, slight. Kidneys show early arterio-sclerotic changes.

Case 15. Female, aged 26 years. History of chorea in childhood, three 'fits' eighteen months before admission, with weakness of right arm and leg, increasing shortness of breath and swelling of ankles for two months.

Admitted 5.1.21. High coloured, cyanosed, orthopnoeic, and dyspnoeic, râles at bases of lungs, heart slightly enlarged, signs of mitral stenosis and regurgitation, liver greatly enlarged and tender. Pulse 114. Respirations 24. Urine: albumin 1 per cent.; no casts, red blood-corpuscles, &c.

4.2.21. Greatly improved. Pulse 80. Respirations 20. Orthopnoea, but little dyspnoea. Liver still enlarged, but not tender. Lungs clear, no oedema of ankles. Is able to be up. No albumin in urine. Subsequent history: 26.3.21. Readmitted with auricular fibrillation. Died at home, July, 1921.

Case 16. Female, aged 39 years. History of severe sore throat at 16 years, and of attacks of 'rheumatic' pains in feet since. Onset of shortness of breath and palpitation one year before admission; much worse, with swelling of feet two months before admission.

Admitted 22.1.21. Very cyanosed and slightly icteric, orthopnoeic and extremely dyspnoeic, râles at bases of lungs, oedema of legs and back, ascites, liver large and tender, heart enlarged, signs of mitral regurgitation and stenosis.

Auricular fibrillation. Ventricular rate 160. Radial pulse 140. Respirations 40. Urine: albumin—a trace.

9.2.21. Improved. Respirations 22. Pulse 70, no deficit. Oedema as before. No albumin in urine.

2.3.21. Pulse 90, no deficit. Oedema less. Diuresis has commenced. Respirations 24.

25.3.21. Commencing to get up. Still orthopnoeic. Pulse 76, no deficit. Respirations 24. Only slight oedema of ankles now. Liver smaller and not tender. Dyspnoeic on slightest exertion.

Case 17. Female, aged 42 years. History of repeated attacks of acute rheumatic arthritis since the age of 12 years, shortness of breath, palpitation, and swelling of ankles since November, 1919.

Admitted 8.3.21. Pale, cheeks flushed, cyanosis of lips, orthopnoea, severe dyspnoea, oedema of ankles, ascites, râles at bases of lungs, liver and spleen enlarged, signs of mitral stenosis and regurgitation. Pulse 120. Respirations 40. Infective endocarditis suspected but not confirmed.

20.4.21. Improved. No cyanosis or oedema. Dyspnoea less. Liver still enlarged. Spleen not palpable. Pulse 70 as a rule, but during arterial puncture was 100. Respirations 24. Is able to be up.

Case 18. Female, aged 45 years. No history of rheumatism or other aetiological factors; was quite well until October, 1920, when she had a sudden attack of abdominal pain and shortness of breath, with swelling of feet a few days later.

Admitted 21.4.21. Cheeks flushed, cyanosed, orthopnoeic, moderately dyspnoeic. Slight oedema of ankles, râles at bases of lungs, liver enlarged, heart enlarged, signs of mitral stenosis and regurgitation. Auricular fibrillation. Ventricular rate 160. Radial pulse not palpable. Respirations 24.

4.5.21. Greatly improved. Pulse 70, no deficit. Still orthopnoeic, slight dyspnoea, lungs clear, no oedema of ankles.

Case 19. Male, aged 56 years. History of pains in chest and shortness of breath since 1914, and gradually increasing.

Admitted 18.4.21. Anxious expression, orthopnoeic and extremely dyspnoeic with Cheyne Stokes's breathing, difficulty in swallowing, oedema of ankles, cyanosis varying with respiratory activity, heart greatly enlarged with signs of a large thoracic aneurysm and aortic valve involvement. Aneurysm confirmed by X-ray. History of syphilis.

25.4.21. Much easier and respiratory distress less. Pulse 76. Respirations 32. Cheyne Stokes's breathing still present.

Case 20. Male, aged 45 years. History of hemiplegic attack 21.1.21 and gradual improvement, during which attacks of dyspnoea appeared and increasing shortness of breath.

Admitted 24.10.21. Pale, orthopnoeic, slightly dyspnoeic, heart enlarged and hypertrophied, signs of aortic incompetence and dilatation of aorta. Blood-pressure 250–120. X-ray shows diffuse aneurysmal dilatation of arch of aorta. Blood urea (30.10.21) 100 mg. per 100 c.c. Wassermann reaction positive.

9.11.21. Slight dyspnoea during arterial puncture.

12.11.21. Attack of acute dyspnoea and angina.

14.11.21. Signs of pericarditis, and feels much better; probably haemopericardium.

28.11.21. More comfortable; no further attacks of dyspnoea.

Case 21. Male, aged 27 years. Porter. History of repeated attacks of acute bronchitis since 1918. January, 1920, swelling of legs and abdomen in addition to bronchitis, and urine scanty.

Admitted 13.11.20. Temperature 100° F. Pulse 110. Respirations 24. Cyanosed, orthopnoea, and severe dyspnoea with oedema of face and ankles. Signs of diffuse bronchitis. Heart dilated and systolic murmur in tricuspid area. Urine 250–750 c.c. Albumin 0·5 per cent; red blood cells, hyaline and granular casts. Blood-pressure 96–80.

20.11.20. Blood urea 73 mg. per cent.

26.1.21. Blood urea 40 mg. per cent. Gradually improved, and discharged 8.2.21 with no signs of cardiac damage, no oedema, and only a few rhonchi in lungs. Trace of albumin in urine.

Case 22. Male, aged 55 years. Boot-black. History of headache, shortness of breath, and swelling of feet for two weeks. Cough for many years, and alcoholic excesses.

Admitted 13.11.20. Temperature 98·4° F. Pulse 70. Respirations 30. Pale, face puffy, cyanosed, orthopnoea, and breathing rapid and shallow. Signs of emphysema and bronchitis. Râles at bases of lungs, liver enlarged, oedema of ankles and hands. Blood-pressure 190–95. Urine 1,500–2,000 c.c. Albumin 0·075 per cent.; specific gravity 1,010; no red blood cells, no casts.

15.11.20. Blood urea 140 mg. per cent.

20.11.20. Blood urea 84 mg. per cent. Symptoms gradually disappeared and patient was discharged 22.12.20.

Case 23. Male, aged 23 years. French polisher. History of swelling of face and legs in November, 1918, and unable for work since. Several relapses.

Admitted 17.5.21. Temperature 97° F. Pulse 100. Respirations 24. Pale, face puffy, cyanosed. Heaving cardiac impulse. Blood-pressure 216–105. Urine: 1,500–2,000 c.c. Albumin 1 per cent; hyaline, granular, and cell casts, red blood cells.

28.5.21. Blood urea 270 mg. per cent.

30.5.21. Drowsiness and grouped breathing.

31.5.21. Convulsion.

3.6.21. Died. Autopsy: chronic diffuse nephritis.

Case 24. Female, aged 33 years. Housewife. History of weakness, diminished urine, and pain in back since June, 1920. Perianal abscess April, 1921.

Admitted 21.6.21. Temperature 97° F. Pulse 84. Respirations 18. Pale, thin woman, tongue furred, and breath foul. Nothing abnormal in heart and lungs. Liver and spleen enlarged. Blood Wassermann positive. Urine: 1,000–2,000 c.c. Albumin 0·7 per cent.; few red blood cells and granular casts.

27.6.21. Blood urea 180 mg. per cent. Refused treatment and discharged herself. Died several weeks later.

Case 25. Female, aged 27 years. Housemaid. History of fever and breathlessness in January, 1921, followed by swelling of face and legs. Similar attack in December, 1920, with a discharge from the ears.

Admitted 1.2.21. Temperature 97° F. Pulse 68. Respirations 18. No orthopnoea, no cyanosis, no oedema. Nothing abnormal in heart and lungs, except a heaving cardiac impulse. Blood-pressure 140–85. Urine: 1,000–2,000 c.c. Albumin 0.075 per cent.; few red blood cells and granular casts. Blood urea 140 mg. per cent.

9.2.21. Breathing stertorous. Rash on forehead and chest diagnosed as 'uraemic' by Sir Archibald Garrod. Blood urea 356 mg. per cent. Vomiting. Bled, and large quantities of alkalis given intravenously and by the mouth. Breathing became natural, but urea retention increased, and a severe anaemia developed.

12.3.21. Red blood cells 950,000.

14.3.21. Died. Autopsy: kidneys showed advanced chronic interstitial nephritis.

Case 26. Male, aged 45 years. Labourer. Gradual onset of weakness and shortness of breath in the Army in 1918. Had been A 1 on enlistment, and was discharged B 3 because of his heart. No previous illnesses.

Admitted 24.1.21. Pale muddy complexion. Moderate orthopnoea and dyspnoea. Heart enlarged, and signs of mitral and aortic regurgitation, and there was a short musical systolic murmur at the apex in addition. Râles at bases of lungs. Liver and spleen both enlarged. No oedema of face or ankles. Blood Wassermann negative. Urine: albumin 0·05 per cent.; granular and hyaline casts, red blood cells. Blood culture, no growth on several occasions.

1.2.21. Blood urea 150 mg. per cent.

4.2.21. Delirious, and later comatose. Oedema of face and ankles. Given large quantities of alkali by mouth.

5.2.21. Blood urea 505 mg. per cent. Treated with subcutaneous injections of caffeine, and gradually improved.

4.3.21. Blood urea 160 mg. per cent. An abscess developed at site of a subcutaneous injection showing *Staphylococcus aureus*, and further abscesses developed in all parts of body. When discharged—21.6.21—at his request, he was still developing abscesses, but his general condition was unchanged. Died at home October, 1921.

Case 27. Male, aged 28 years. Motor driver. History of increasing shortness of breath and cough since June, 1919, becoming much worse for five weeks before admission, when pain and swelling of joints developed. Scarlet fever at 9 years.

Admitted 3.5.21. Temperature 99° F. Pulse 110. Respirations 28. Cyanosed, oedema of face and ankles, clubbed fingers. Heart enlarged, and signs of mitral and aortic regurgitation. Urine: 800–1,000 c.c. Albumin 0·4 per cent.; granular and hyaline casts, red blood cells. Liver and spleen enlarged and tender. Blood culture, no growth. Blood urea 94 mg. per cent.

9.5.21. Blood urea 140 mg. per cent.

12.5.21. Purpuric eruption.

18.5.21. Sore throat. Diphtheric bacilli found.

22.5.21. Died. Autopsy: vegetations on aortic and mitral valves, which were thickened and stenosed. Kidneys showed chronic parenchymatous changes as well as the 'flea-bitten' lesions of infective endocarditis.

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AN INQUIRY INTO THE MORE REMOTE PROGNOSIS IN WAR NEPHRITIS

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THIS inquiry was undertaken with a view to throwing some light upon the more remote prognosis in that particular form of acute nephritis which was so common in the armies on the Western Front during the War. It is hoped, however, that the conclusions arrived at may not be without bearing upon the problem of the prognosis in acute nephritis as met with in civil life.

A part of the facts to be detailed is derived from the study of the after-histories of a series of patients, who were observed while in the acute stage of war nephritis at a base Hospital in France early in 1917, and whose progress up to the middle of 1921 it has been possible to follow, through the kindness of the Ministry of Pensions and the Medical Research Council. Further interesting facts relative to the prognosis generally in this condition have been supplied by the Ministry of Pensions from their very extensive records.

The directly observed material consists of about 125 cases, all of which came under observation by the writer within a few days of the onset of the condition and remained under personal supervision for from one to six weeks. These were all indubitable cases of acute nephritis, all characterized by oedema, albuminuria, and haematuria, though the extent of these symptoms differed very greatly from case to case. For the purposes of this investigation 100 perfectly typical cases have been taken at random out of this series of 125 and, with the assistance of the Ministry of Pensions, their after-histories up to the middle of 1921—a period of about 4½ years from the onset—followed as closely as possible.

First, as to mortality rate: of these 100 cases, it was found that by the middle of 1921 three had died. One of these was aged 37 and the remaining two 26 and 29 respectively. From such a small number, however, it is impossible to make any deduction as to the effect of age on the prognosis in regard to death. One of these patients died of scarlet fever, with which he became affected while yet in hospital, and died within nine months of the onset of the nephritis. A fatal issue in scarlet fever is so rare in a patient of this age, that it seems justifiable to attribute his death largely to the renal condition. Some interest attaches to this case in view of the suggestion, made at the time when war nephritis was the subject of a good deal of attention, that every case should be regarded as a part of, or as the result of, an undiagnosed attack of scarlet

fever. A second attack of scarlet fever is a rarity and, at so short an interval, a high improbability. The cause of death in the remaining two cases is specified as 'nephritis' and appears to have occurred as the result of acute exacerbation of the renal condition. No information was to be had as to the state of the kidneys at death. The period from onset of the fatal termination in these cases was 18 and 27 months respectively.

Of the remaining 97 cases, 65 were eventually returned to duty, but of these 2 had recurrences while serving in France, and finally became pensioners from the condition. The remaining 32 were discharged as unfit.

At all ages, then, the immediate disposal of 100 cases was as follows:

TABLE I.

Returned to duty	65 %
Discharged unfit	32 %
„ „ (later died)	3 %

On breaking up the cases into two age groups of under and over 35 years respectively, the following figures are obtained:

TABLE II.

	Under 35.	Over 35.
Returned to duty	44 = 66·6 %	21 = 61·7 %
Discharged unfit	20 = 30·3 %	12 = 35·4 %
„ „ (later died)	2 = 3·1 %	1 = 2·9 %
	66 = 100 %	34 = 100 %

It is noteworthy that the percentage of those returning to duty in the category under 35 is higher by 4·9 per cent. than in that for those over that age; the percentage of those discharged unfit is correspondingly higher among those over than under 35. This is an intimation that the immediate prognosis as regards degree of recovery is better under than over the age of 35.

Evidence as to this unfavourable influence of increasing years upon the general outlook becomes stronger on further inquiry.

With a view to ascertaining the rate at which and the degree to which recovery takes place in this condition, the histories of all those who still were or ever had been in receipt of a pension were obtained, through the kindness of the Ministry of Pensions. With six exceptions, those of whom the Ministry of Pensions had no record were those who had been restored to health and returned to duty. These six exceptions were men who, at the termination of their stay in hospital, were discharged as unfit, but who had never been awarded a pension. For the purposes of this inquiry they are regarded as being only 'partly fit', but not actually 'invalid', and are included in the second class described below.

In order to simplify matters in gauging degree of recovery, this is considered in three grades. In Class I are included all those cases in which, after the cessation of hospital treatment, the restoration to health was regarded as complete—this being evidenced during the war by the return of the patient to duty, and, after demobilization, by the fact that no pension, or one of under 20 per

cent., was awarded. Under Class II are included those cases in which, though the return of health was not complete, the patients did not actually remain invalid, the criterion for this being the award of a pension of from 20 per cent. to under 60 per cent. The six patients mentioned above as having been discharged unfit but awarded no pension are arbitrarily included in this class throughout the period under consideration. Class III comprises all cases actually invalid, as evidenced by receipt of a pension of from 60 per cent. to 100 per cent., or by the fact that the patient remained under full hospital treatment. Class IV consists of those who died in the period under consideration. On the chart drawn up on this basis the classes are designated as follows: Class I = fit, Class II = partly fit, Class III = invalid, Class IV = dead.

The actual figures on which the chart is compiled are as follows:

TABLE III.

All Ages.	End of 1917	1918	1919	1920	1921
Class I (fit)	68	74	73	77	79
Class II (partly fit)	24	18	23	18	17
Class III (invalid)	7	7	2	3	1
Class IV (dead)	1	1	2	2	3
			100		

These figures show the speedy recovery of the majority, 68 per cent. of the cases; all of which had terminated in complete recovery by the end of twelve months from the onset of the condition. They further show that, in those cases in which complete restoration to health had not taken place at the end of twelve months, there is a marked tendency for the condition to take on a chronic form. Thus by 1921, at the end of four and a half years from the onset, only 11 per cent. more cases had attained to full recovery, leaving 17 per cent. partly fit and 1 per cent. invalid, while 3 per cent. were dead.

Of the 100 cases considered above 34 were over and 66 were under the age of 35 years. The course in these age groups is shown below.

TABLE IV.

Over 35.

	End of 1917.	1918.	1919.	1920.	1921.
Class I	21 = 61·8 %	23 = 67·6 %	24 = 70·6 %	25 = 73·5 %	25 = 73·5 %
Class II	10 = 29·2 %	9 = 26·4 %	9 = 26·4 %	7 = 20·5 %	8 = 23·5 %
Class III	3 = 9·0 %	2 = 6·0 %	1 = 3·0 %	2 = 6·0 %	0
Class IV	0	0	0	0	1 = 3·0 %
			34 = 100 %		

TABLE V.

Under 35.

	End of 1917.	1918.	1919.	1920.	1921.
Class I	47 = 71·2 %	51 = 77·2 %	49 = 74·1 %	52 = 78·7 %	54 = 81·7 %
Class II	14 = 21·2 %	9 = 13·6 %	14 = 21·2 %	11 = 16·6 %	9 = 13·6 %
Class III	4 = 6·0 %	5 = 7·6 %	1 = 1·6 %	1 = 1·6 %	1 = 1·6 %
Class IV	1 = 1·6 %	1 = 1·6 %	2 = 3·1 %	2 = 3·1 %	2 = 3·1 %
			66 cases = 100 %		

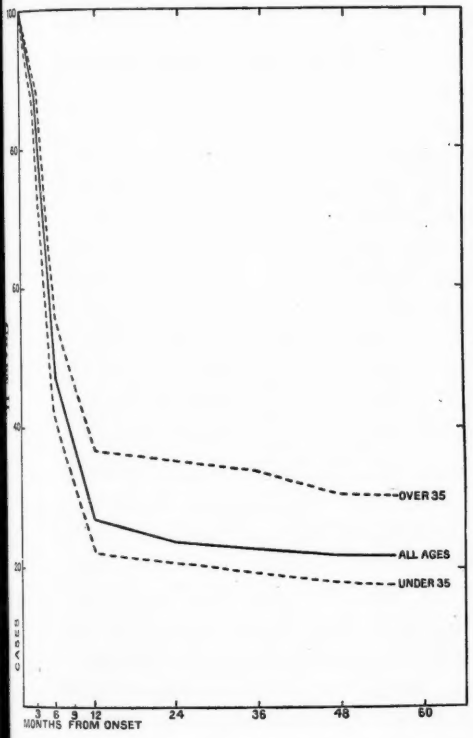
These figures again indicate the better outlook in patients under, as compared to over, 35 years of age. Thus it will be noted that, whereas at the end of the first twelve months from the onset in patients under 35, 71·2 per cent. fall under Class I, and at the end of 4½ years as many as 81·7 per cent.—in men over that age these corresponding figures are only 61·8 per cent. and 73·5 per cent.

The accompanying chart (I) is an attempt to express graphically the figures contained in Tables III, IV, and V. The chart is divided under 5-year headings from 1917 to 1921, the state of the cases at the end of each year named forming the basis of the chart, with the exception of 1921, for which year the state has only been followed up to June or July. Under each year heading are four groups of three columns each. The first group of columns shows the cases falling under Class I, the second in Class II, the third in Class III, and the fourth in Class IV. Of the three columns in each group the first is compiled on the actual figures for cases at all ages as shown in Table III. The numbers represented by the height of the columns can be read from the scale to the left. The second and third columns show the condition of cases over and under 35 years of age respectively, these being calculated as a percentage of the total number in each group as in Tables IV and V.

The interesting features of the chart are the progressive, though slow, increase in the height of the columns representing Class I, and the corresponding decrease in height of the columns standing for Class II, also the general preponderating height of the under 35 column in Class I over that for cases over that age, and the reverse arrangement under Class II. The significance of these points has been remarked on in considering the tables from which the chart is drawn.

In Chart II an attempt has been made to represent graphically the duration of convalescence at all ages and in the age groups already described. In the plotting of the charts, the 97 cases described above, in which death had not taken place, were used, to which were added the three next in sequence in the case sheets, so as to bring the total up to 100. It is to be remarked that of cases at all ages about 40 per cent. have completed their convalescence at the end of six months and about 70 per cent. by the end of one year from the onset. Furthermore, it is noteworthy that from the end of twelve months on to the termination of the time of observation, the curve tends to become parallel with the base-line, indicating, as pointed out above, that in those cases in which recovery is not complete by the end of twelve months, there is an overwhelming tendency for the condition to become chronic. The unfavourable effect of advancing age on the course is again clearly shown by the relative position of the curves for cases over and under 35 years of age. These curves are plotted on the percentages of the numbers of the cases falling in each of these age groups.

The condition of those cases still in receipt of a pension, as shown by notes taken at their more recent boards, suggests that the condition was in course of becoming of that type usually classified as 'chronic Bright's disease', or that this stage had already been reached. Thickening of the arteries, anaemia, and polyuria are frequently noted; the specific gravity of the urine, when mentioned,


OVER 35
ALL AGES
UNDER 35
CASES
3 6 9 12 24 36 48 60
MONTHS FROM ONSET

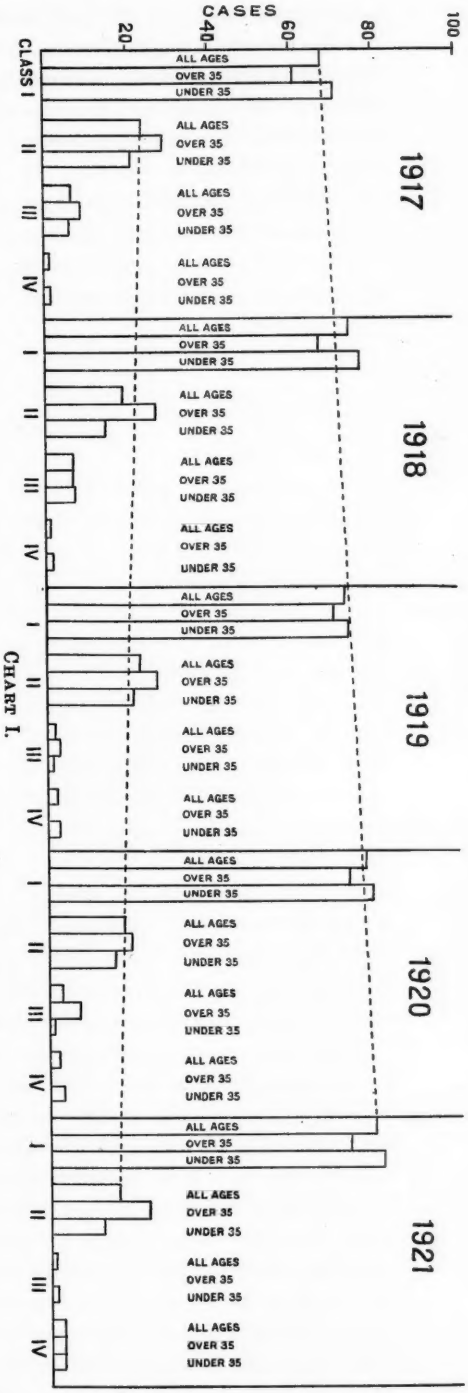

CASES
20 40 60 80 100
CLASS I II III IV
ALL AGES
OVER 35
UNDER 35
1917
1918
1919
1920
1921

CHART I.

is low, from 1,001 to 1,006; albuminuria is frequently stated to be present, but usually only to a slight degree; puffiness of the eyes and occasional swelling of the ankles are frequently commented on. It is interesting that, although an atheromatous condition of the arteries is definitely noted to be present in a large proportion of the cases, the blood-pressures, where recorded, are not high. The highest mentioned is 165 mm. Hg, but for the most part they run from 135 to 145 mm. Hg. So far as this evidence goes, it suggests that the arterial thickening preceded the increased blood-pressure and did not occur as a result of it.

In twenty-five cases, in which the notes were fairly full, the relative frequency of occurrence of the symptoms most often commented on was as follows:

Arterio-sclerosis	11	
Oedema (including puffiness under eyes, &c.)	9	
Albuminuria	7	
Specific gravity of urine under 1,005	5	(of only 5 cases in which estimated)
Cardiac enlargement	2	
Accentuated second heart sound	2	
High-tension pulse	2	

An attempt to ascertain if any particular symptom at the onset or during the acute stage had any marked effect on the prognosis was quite without result. Of two cases in the series which showed clinical evidence of 'uraemia' in the sense of convulsions or coma, both recovered completely and returned to duty within six months of the onset. One was killed in action about eight months from the onset of the nephritis; the other, who, while in a comatose condition, had 120 mg. per 100 c.c. of urea in his blood, was wounded in action about one year from the onset of the nephritis and is now in receipt of a pension for his wound. The three cases that ended fatally were of the most diverse types—two were clinically mild, when seen in France. One of these gave a history of a previous attack of renal disorder; the other had a curious oedema, localized to the scalp, and showed only a slight albuminuria and only traces of blood in the urine; this was the case in which the determining cause of death was scarlet fever. The third case was clinically severe, of the so-called 'lower tract' type, with much oedema, albuminuria consistently to the extent of over 1·2 per cent. (Esbach), and intense haematuria. Of the cases which rapidly recovered, some were clinically severe at the onset, others quite mild, and exactly the same applied to those which ultimately became chronic. If any generalization can be made, it is that those cases which showed a high degree of albuminuria, to the extent of 1·2 per cent. (Esbach), or over, for over two weeks on end, tended to do badly.

No extended series of figures exist on which the death-rate of all those who have suffered from war nephritis can be calculated. The Ministry of Pensions, however, has been kind enough to estimate the death-rate among those pensioned for the condition, which, it must be borne in mind, is a very different thing from those who have suffered from it. Among nephritis pensioners the approximate death-rate is 24 per 1,000 per annum. Among the civil population of about the age of 35, it is 8 per 1,000 per annum; and among pensioners from all causes, 11 per 1,000 per annum. The expectation of life of pensioners from war nephritis is thus less than half that of other pensioners.

These figures were so interesting, that the Ministry of Pensions kindly undertook a further inquiry, as to the cause of death among nephritis pensioners. It then became evident that less than half such deaths were directly attributable to nephritis. Actually it was found that of nephritis pensioners only 11 per 1,000 per annum died of renal conditions, while 14 per 1,000 per annum died from other causes.

These results were arrived at by the consideration of the causes of death in a series of 346 deaths of nephritis pensioners. These were as follows:

TABLE VI.

From nephritis		163 = 47·1 %
From pulmonary tuberculosis	31 = 8·9 %	
From respiratory conditions other than T.B. . .	28 = 8·10 %	
From circulatory conditions	54 = 15·6 %	
		113 = 32·6 %
From other causes (including accident and violence)		70 = 20·3 %
		346 = 100 %

The above figures make it evident that a fatal issue, in which the main feature is renal, is by no means the rule in sufferers from war nephritis in its chronic form. In only 47·1 per cent. of such patients is death finally determined by the state of the kidneys. In 32·6 per cent. of cases the outstanding features among the symptoms at the close of life are either circulatory or respiratory. The circulatory disturbances have come to be looked upon as intimately associated with renal disorder—whether in the light of cause or effect—but that respiratory conditions should play so large a part in determining a fatal issue comes as something of a surprise. The large proportion of deaths from pulmonary tuberculosis, which make up 9 per cent. of the total, is particularly noteworthy.

Conclusions.

The following conclusions are drawn from the facts presented above:

1. That 70 per cent. of cases of war nephritis at all ages terminate in complete recovery before the lapse of twelve months from the onset.

2. That the proportion of cases so terminating in recovery is slightly higher under the age of 35 than over that age.

3. That of cases not fully restored to health by the end of twelve months from the onset, the great majority become chronic.

4. That the occurrence of clinical symptoms of 'uraemia' at the onset has no unfavourable significance as regards the later prognosis.

5. That in cases becoming chronic, there is a tendency for a fatal issue to be determined by circulatory or respiratory conditions.

6. That the proportion of deaths from pulmonary tuberculosis among patients in the chronic stage is high.

Although frequent references have been made by many writers to the immediate prognosis in war nephritis, observations on the later course of this

condition are not numerous. Early in the war Osler (1) cautioned against giving too favourable a prognosis. Abercrombie (2) has reported on the after-histories of 171 cases for periods of from twenty-four to thirty-two months from onset; his observed mortality at all ages for that period is 3 per cent., the same as that arrived at above. The after-histories up to one year from onset of 50 of the cases considered above were analysed by the present author (3) in 1918, when the more unfavourable prognosis over the age of 35 was noted, and certain deductions were also made as to the influence on the prognosis of the date of disappearance of oedema and albuminuria. Howard-Tasker (4) observed 37 cases up to seven months from onset; he found that by that time 50 per cent. had recovered; another 25 per cent. might still do so, while the remaining 25 per cent. had developed chronic nephritis.

My thanks are due to Professor H. MacLean for advice and criticism; to the Medical Research Council, without whose assistance the inquiry could not have been carried out; and to the officials of the Ministry of Pensions, for their unfailing courtesy and readiness to aid, when put to trouble, I fear, entirely incommensurate with the use that I have been able to make of their labour.

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SYPHILIS OF THE STOMACH

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With Plates 8 and 9

Introduction.

Syphilitic lesions of the stomach have always been regarded as extremely uncommon, and in British medical literature the subject has attracted comparatively little attention. Even Jonathan Hutchinson, with his enormous experience, states in his text-book on syphilis, published in 1887, 'I do not know of any museum specimens, nor of any published observations (of syphilis of the stomach), but I have witnessed, in a single case, most distressing stomach pain after food in association with extensive syphilitic induration of the tongue'. A short search, however, through American, French, and German records of visceral syphilis has shown the existence of many more authentic examples of the condition than is perhaps commonly known.

In France the relation of syphilis to certain cases of gastric disease has been fully recognized, and the French view of the matter has recently been brought to notice in this country in a lecture by Monod (1921). In the discussion following this lecture, Turnbull (1921) (13) stated that in a personal experience of nearly 13,000 autopsies at the London Hospital since 1907 he had met with only one case which might possibly be regarded as syphilis of the stomach, although even in this case the proof was not completely established. This seems to agree with the experience of other large pathological laboratories in this country.

Recently the opportunity has occurred of investigating fully a very typical case of an important variety of gastric syphilis, unique, or almost unique, from the fact that abundant spirochaetes were found in the lesion. The confusing clinical signs, and the very complete pathological examination made in this case, seem to warrant its publication in full.

For comparison of this case with others of a similar kind, a brief account is also given of some of the chief records of syphilis of the stomach in this and other countries.

[Q. J. M., April, 1922.]

Historical.

It is generally recognized that the diagnosis of gastric syphilis during life has hitherto been difficult. Many more cases have been seen and described after autopsy than have been recognized and reported during life. In the earlier literature an uncertainty in the diagnosis, which was perforce based on histological evidence only, exists in many instances; and, as would be expected, the discovery of the causal organism by Schaudinn and Hoffmann (1905) and the introduction of the Wassermann reaction (1906) place all the later reports on a more definite footing.

In the older literature the pathological diagnosis of one variety of gastric syphilis is fairly certain, from the definite characters of the lesion both macroscopically and histologically. This is the condition of submucous gumma, breaking down as a rule to cause ulceration. In the case of other varieties of the disease the diagnosis, even in the presence of obvious signs of syphilis elsewhere, must always be open to doubt, since many of the histological changes found in syphilis (round-celled infiltration, endarteritis obliterans, and cellular necrosis) are found in other granulomata, and in many chronic inflammatory lesions. This point is emphasized in a case reported recently by Fowler (1921) of a woman known to have signs of gastric ulcer of long standing, but suffering from secondary syphilis when examined. A course of antisyphilitic treatment did not lead to improvement, while gastro-enterostomy afforded short relief. Finally the pyloric half of the stomach was resected, and a large callous ulcer, adherent to the pancreas, was found. In this case obviously a very chronic round ulcer of the stomach was present, having no relation to the presence of syphilis. The syphilitic infection, however, was only at the secondary stage, whereas the great bulk of the syphilitic lesions of the stomach on record have been *late* manifestations of the disease. We as yet know little of the effects on the stomach of early syphilis. Chiari (1891), in a series of autopsies on 243 cases of known syphilis, found lesions of the stomach in two cases only. In one of these the disease was inherited, and in the other acquired. Quite recently Stoeckenius (1921) has described in great detail the results of very careful and extensive histological examination of the organs from four cases of recent syphilis in young adults. In all of them the amount of granulomatous tissue found scattered through the various organs was very great, so that in three of the cases tuberculosis was at first suspected. Damage to blood-vessels was also prominent, and although the stomach is not dealt with apart from the intestinal tract generally, these observations do at least suggest the possibility of early syphilitic lesions of the stomach.

Before the discovery of the spirochaetal cause, and the use of the Wassermann test, cases of gumma of the stomach form the bulk of the literature on the subject. The most quoted early paper is that of Chiari (1891), who reported the two cases already referred to. He accepts as authentic the cases described by Klebs (1869), Cornil and Ranvier (1884), and Birch-Hirschfeld (four cases—1887). Monod

(1921) traces the French writings on the subject as far back as 1834, and refers to the thesis of Pater (1907), who collected records of 122 cases.

S. Flexner (1898) described a very typical case of syphilis of the stomach, of gummatous nature, which bears very close resemblances to the example now discussed. The patient was a man of 52 years, who died from perforation of the stomach with resulting peritonitis. A large gumma of the liver was found at autopsy, and the stomach showed a large ulcer (5 × 5 cm.), situated close to the cardia. Very careful histological examination of the ulcer was made, and changes of two distinct types determined. The earlier lesion consisted of a cellular infiltration of the submucosa with cells of granulation tissue type. Foci of necrosis had occurred within large collections of these cells. The second and later type of lesion was more common, and was found in all parts of the ulcer, including the tissues forming its elevated borders. It consisted of dense fibrous tissue formation, containing scattered granulation tissue cells. In this tissue also the blood-vessels showed extensive damage, endarteritis and endophlebitis obliterans, and hyaline thrombosis with organization, being very prominent.

E. Fraenkel (1899) described a remarkable case, seen in 1895. A man of 47 years was admitted suffering from diarrhoea and pain in the abdomen, and died from peritonitis following acute perforation. In the stomach thirteen ulcers were present, along with thirty-one others scattered along the small intestine. The possibilities of enteric fever and tubercle were fully considered, but a diagnosis of syphilis was finally decided on after very careful histological examination of the ulcers.

Soltau Fenwick (1901) recognized the occurrence of gastric syphilis, and claimed that about 5 per cent. of chronic gastric ulcers are of syphilitic origin. Other writers have attributed an even larger number of chronic ulcers of the stomach to syphilitic infection, Ewald (1905), for example, placing 10 per cent. of gastric ulcers in that category.

Turning to the more recent publications on gastric syphilis, the comprehensive paper by Monod (1921) has already been referred to. The most complete recent review of the subject is probably that of Wile (1920), in America, who gives a list of over fifty references to other writers. He states that he himself has seen three cases of gumma of the stomach in a period of four years. Smithies (1915) has reported an analysis of 7,545 patients suffering from all types of dyspepsia, among whom 26 gave a positive Wassermann reaction. Of the patients (1,603 in number) who showed evidence of definite organic disease in the stomach or duodenum, a proportion of 1·6 per cent. gave a positive Wassermann reaction. It appears to be quite unfair, however, to suggest that in the latter patients the gastric symptoms were necessarily due to syphilis, and not merely coincident with it.

Among other recent writers, Haas (1920) describes a case of 'syphilitic tumour' of the stomach, and Florand and Girault (1921) give a description of a large tumour in the epigastrium which at operation was discovered to be

a gummatous mass involving both the liver and stomach. Other examples are also referred to later in the text.

Varieties of Gastric Syphilis.

All writers are agreed that the commonest form of gastric syphilis arises as a submucous gumma, which tends to undergo the usual degenerative changes, and finally leads to ulceration. This variety has added importance from the fact that many more of such cases have been diagnosed as carcinoma of the stomach and treated as such, than as syphilis. A palpable tumour of varying size is always found on examination. Just as in carcinoma, loss of weight and marked cachexia are the rule, and examination of the gastric contents adds a further source of error in diagnosis, which is dealt with later.

Apart from gumma of the stomach, which is admittedly uncommon, other varieties of gastric syphilis which have been described must be extreme rarities. Monod (1921) has attracted attention to diffuse syphilitic infiltration as one cause of 'leather-bottle stomach', although there is no doubt that scirrhous carcinoma is a much more common reason for the occurrence of this somewhat rare deformity.

Wile (1920) adopts a very wide classification, which certainly seems to include all the possibilities. The rarity of all other forms when compared with gumma of the stomach is, however, fully acknowledged. His classification is as follows:

I. Gastric syphilis.

(*a*) Syphilitic catarrh.

(*b*) Syphilitic round ulcer.

(*c*) Diffuse syphilitic infiltration of the gastric mucosa, with distortion of the stomach.

(*d*) Pyloric syphilis—including ulcer, cicatrix, gumma, and diffuse infiltration.

II. Perigastric syphilis (with secondary implication of the stomach).

The Relation of Syphilis to the Common Round Ulcer of the Stomach.

It is quite obvious from clinical experience that syphilis has nothing to do with the aetiology of the majority of cases of simple round ulcer of the stomach. The question, however, must be raised whether syphilis may be the cause of even a small percentage of such ulcers. Wile, Fenwick, Smithies, Ewald, and others all believe that syphilis may be a cause of round ulcer. One statement by Wile has a particular interest in this connexion. He says while dealing with round ulcer due to syphilis that 'a recent case at the University Hospital, in Cabot's service, gave a negative Wassermann in the presence of a typical syphilitic ulcer. Spirochaetes were demonstrated by Warthin in the excised material.' This case

does not appear to have been published in full, but, in passing, it may be stated that this would seem to be the only other case, apart from our own, in which spirochaetes have been demonstrated in a syphilitic lesion of the stomach.

On the other hand the case reported by Fowler, and already referred to, shows how chronic round ulcer of the stomach may coincide with, and yet have nothing to do with, a syphilitic infection.

Gastric Analysis in Syphilis of the Stomach.

The occurrence of achlorhydria in the gummatous variety of syphilitic ulceration of the stomach, in contrast to the results of analysis in round ulcer, has attracted attention. The attention is well merited, since the absence of free hydrochloric acid tends to add support to an erroneous diagnosis of carcinoma.

Glaser (1921) deals most fully with the question of gastric analysis in cases which have been diagnosed as gastric syphilis with more or less certainty. He collected for his paper ten cases (including one of his own) in which the results of examination of the gastric contents are recorded. In all of these there was achlorhydria. The same conclusion is arrived at by Hausmann (1911) and Brugsch and Schneider (1915). Glaser also refers to the experiences of Neugebauer (1914), who found that among 200 soldiers suffering from syphilis there was complete absence, or only traces, of free HCl in 18 per cent. This of course introduces another question concerning the effects of early syphilis on the stomach and the variety of gastric lesion called 'syphilitic catarrh' by Wile. Smithies also states, in the statistical study of cases of dyspepsia already referred to, that among twenty-six cases regarded as probably due to syphilis on account of the positive Wassermann reaction, free hydrochloric acid was absent in twenty-four of them.

In our own case gastric analysis showed a complete absence of hydrochloric acid and the presence of lactic acid. Taking into consideration the extent of the damage to the stomach in gummatous ulceration, these results of analysis are not surprising.

The Effects of Antisyphilitic Treatment in Gastric Syphilis.

This is a difficult part of the subject to deal with adequately since the clinical diagnosis is so rarely made with accuracy. It is certain, however, that cases have occurred associated with the presence of a large mass in the epigastrium, in which very rapid cure, with gain in weight and removal of cachexia, have occurred in a few weeks after antisyphilitic treatment.

Hausmann (1911) describes a case of gumma of the stomach, diagnosed clinically by him, and treated with injections of salvarsan. There was a large tumour, involving both the greater curvature and the pyloric region. A history of syphilis was obtained, and the Wassermann reaction was weakly positive.

The tumour had entirely disappeared six weeks after treatment was commenced. A further point of interest recorded in this case is that whereas achlorhydria was noted on admission, free hydrochloric acid began to return two months after treatment began, and a month later the chemistry of the gastric contents was found to be normal.

Pezoldt (1915) reports a typical example of ulcerating gumma of the stomach in a negro, in which complete cure followed within a few weeks after treatment with salvarsan and iodides.

Sherran (1921) has given a brief description of a case of especial interest. The patient had a large tumour of the stomach, thought to be malignant, and with all the characters of a carcinoma. On examining the patient further, however, a swelling was found in the left epididymis, which was diagnosed as of syphilitic nature. The Wassermann reaction was found to be positive. After antisyphilitic treatment, the nature of which is not stated, the tumour of the stomach disappeared completely within three weeks.

Fenwick refers to cases of ulcer of the stomach which were only cured after the use of large doses of potassium iodide or other antisyphilitic treatment, but in these cases the exact nature of the stomach lesion remains uncertain.

It is a curious fact that recent writers, especially of the French School, have supported the claims of the older methods of antisyphilitic treatment (mercury and, more especially, iodides) against the newer salvarsan remedies, in cases of gastric syphilis. This is a matter on which further experience is required.

Record of a Case of Syphilis of the Stomach, in which abundant Spirochaetes were found in the Lesion.

The patient, a clerk aged 57 years, was admitted to University College Hospital under the care of Dr. Sidney Martin, F.R.S., complaining of pain in the chest and abdomen, and of constipation alternating with bouts of diarrhoea. His previous health had been good, and no history of syphilis was elicited. He was pale and emaciated, and stated that he had lost four stone in weight during the past six months. There was considerable pain and tenderness in the left epigastrium, and a tumour could be felt in this region, protruding below the left costal margin. The mass was about the size of a hen's egg, hard, of irregular contour, and moved with respiration. A diagnosis of malignant growth was made. The liver was not enlarged, and no superficial lymph glands appeared to be involved. The gastric contents were examined on two occasions, at twelve days' interval, and on both of these free hydrochloric acid was absent, whilst lactic acid was present. About a month after admission a fairly copious haematemesis (12 oz.) took place, followed by a second very large haemorrhage about a fortnight later. After the second attack the patient collapsed, and gradually became unconscious. Signs of probable perforation of the stomach were also recognized, but in view of the diagnosis of carcinoma which had been made, and the critical state of the patient, an operation was not considered

advisable. Since there appeared so little doubt of the diagnosis of malignant growth, the Wassermann reaction was not carried out.

At the autopsy generalized peritonitis was found, resulting from perforation of the stomach. Apart from the stomach no other organs showed noteworthy pathological changes, and nothing was found suggesting the presence of an antecedent syphilitic infection. The liver was normal in size and free from disease.

On opening the stomach a remarkable condition was found, which at first sight appeared to fit in with diagnosis of gastric carcinoma of scirrhous type. On examining the organ more closely, however, it was seen that the characters of the ulceration were peculiar, while further dissection showed the lymphatic glands draining the gastric area to be small and free from all signs of cancerous invasion. The absence of secondary growth in the liver in the presence of such extensive ulceration also excited notice.

The macroscopic appearances of the inner surface of the stomach are well shown in the photograph (Plate 8, Fig. 1) and may now be described in some detail.

The lesser curvature of the stomach, from a point about one inch below the cardia to the pylorus, is completely ulcerated. The ulcer also extends over a large part of the greater curvature, and this portion has been cut in two in opening the stomach, so that part appears in the upper part of the opened-out specimen and part below. Two perforations are seen in the ulcer on the posterior wall of the stomach, fairly close together, while in two other adjacent spots penetration of the wall is almost complete (Fig. 1, D). The chief characteristic of the ulcer is its irregular shape and greatly thickened borders. The floor is bare, but the margins are covered with shaggy shreds of necrotic tissue, mixed with shreds of tenacious mucus. Only about two-fifths of the stomach wall is free from ulceration.

The stomach wall is greatly thickened in most parts of the floor of the ulcer, except at the points where perforation has ensued. The thickness is fully half an inch in most places, while in relation to the raised margins it is fully three-quarters of an inch. In section the thickened wall has everywhere a dense pearly-white appearance, such as is often seen characteristically in scirrhous carcinoma of the organ. Particular attention may be drawn to one particular area (Fig. 1, C) of the lesion where the process appeared to be more acute and recent than elsewhere. A similar small area was originally present on the extreme upper border of the specimen, but was removed for histological examination. The results of the examination of this portion of the ulcer are dealt with later.

Owing to the peculiar characters of the ulcer, portions from as many situations as possible were removed for histology, without destroying the macroscopic specimen. The results were as follows, and compare closely with those described by Flexner in his very similar case. Flexner's excellent description was of course written long before the discovery of the causal organism of syphilis in 1905.

Sections from the central portion of the ulcer well removed from the raised margins show, in all the paraffin blocks examined, the same type of structure.

Adjacent to the gastric cavity the floor of the ulcer is composed of a thin layer of necrotic fibrous tissue, infiltrated with round cells. Not a trace of the glandular acini, or of the muscularis mucosae, remains. Below this necrotic layer is a thick zone of dense adult scar tissue, with many fibrils and comparatively few cells. Here and there, however, areas of less adult connective tissue occur, with large fibroblasts, and numbers of small thin-walled capillaries. Many of these small vessels are encircled by round-celled infiltration. Embedded in the mass of dense fibrous tissue are a few arterial trunks, some of them very close to the surface of the ulcer. The walls of these arteries are thickened, and show an advanced stage of endarteritis obliterans, but no thrombosis (Plate 9, Fig. 3). The accompanying veins have also thickened walls, but there is no definite endophlebitis. Hyaline thrombosis is not seen. Thick strands of firm fibrous tissue are also seen to have penetrated from the main mass into the muscular coat of the stomach, so as to interrupt the plain muscle fibres in all directions. In the midst of some of these strands of fibrous tissue, small collections of atrophic and disintegrating muscle fibres are visible. The blood-vessels in the muscular coat do not exhibit thickening, endarteritis, or thrombosis.

In blocks of tissue taken from other parts of the ulcer, especially from the greatly thickened borders, the histological changes are of a very much more active kind. The whole of the mucosa and submucosa is entirely replaced by an actively growing granulation tissue, which is necrotic and shaggy on its surface. The granulation tissue shows abundant fibroblasts, and thin-walled capillaries running up towards the surface (Fig. 4). The whole tissue is also densely infiltrated with cells of lymphocytic type. Wide branches of the granulation tissue extend into the muscular layers of the organ, following for the most part the track of the larger blood-vessels, and separating widely the strands of muscle fibres. In other situations the muscular coat appears to be intact, and the only change noted is the presence of round-celled infiltration along the blood-vessels. The arteries and veins in relation to these actively proliferating granulomatous parts of the ulcer are entirely free from endarteritis. In a few places large masses of granulation tissue have necrosed and separated, so as to expose even the deeper layers of the muscular coat. It is easy to see how in this way perforation must have occurred, and since the main blood-vessels have not undergone endarteritis obliterans the reason for the two attacks of haematemesis is not far to seek.

Other sections from the ulcer show almost all the intermediate stages between the actively growing granulomatous lesion and the almost obsolete zone of scar tissue in the centre, so that it is quite easy histologically to follow the whole course of the pathological process.

No giant cells are seen in any of the sections examined. Except for the very localized and deep patches of necrosis which reach down to the muscular layers, the tissues below the superficial floor of the ulcer are free from degenerative changes and caseation. The subperitoneal connective tissue is in most places greatly thickened behind the area covered by the ulcer, the loose connective tissue

normally found there being converted into dense fibrous tissue, containing many fibrils but comparatively few cells.

At certain parts of the edge of the ulcer, on the greater curvature of the stomach, the margins are not notably raised and thickened, and the site of origin of the lesion is more easily traced. Here the early pathological changes are seen spreading in the submucosa only, below an intact muscularis mucosae, but much altered mucous membrane. The early stage of the lesion consists of large and dense collections of small round cells encircling the blood-vessels, with, in a few places, the development of small patches of granulation tissue. An appearance difficult to explain is the occurrence immediately below the mucosa of several oval nodules of very dense and almost hyaline fibrous tissue, so perfectly circumscribed as to resemble small fibromata.

In the parts of the stomach wall which are free from ulceration (e. g. near the cardiac end) the mucous membrane shows an interstitial gastritis of atrophic type (Fig. 5). The glands are shortened, incomplete, and run in all directions. They are embedded in interstitial tissue which contains many small round cells. Some glandular acini are distended to form small cysts filled with mucus. The blood-vessels in the submucosa are not altered, but are frequently surrounded by collections of small cells of the usual type.

The lymphatic glands draining the stomach posteriorly were also examined histologically, but exhibited nothing more than the catarrhal changes commonly found in the neighbourhood of any chronic inflammation.

Examination for Spirochaetes.

In view of the histology of the lesion as described above, the conclusion was arrived at that the lesion was of syphilitic nature, but it was felt that even more convincing proof would be given if spirochaetes could be demonstrated in the actively growing parts of the lesion. For this purpose eight small blocks of tissue, from known situations, were treated by Levaditi's silver method.

In sections from one block only, spirochaetes were discovered in great numbers penetrating deeply in the actively growing granulomatous tissue. Near the free surface the spirochaetes in the necrotic surface layer were mixed with other organisms, but in the deeper granulation tissue close to the muscular coat they were unaccompanied by any other demonstrable organism. They had the typical appearances of *Tryponema pallidum*, having from eight to fourteen small and regular curves (Fig. 2). The part of the ulcer from which the block containing the spirochaetes was obtained differed in some important respects from other areas of the ulcer. It was reddish in colour, and sharply marked off from the neighbouring parts of the floor. Another area of exactly similar character is well shown in the photograph of the specimen (Plate 8, Fig. 1, c).

Conclusions.

1. The case recorded illustrates the chief clinical and pathological facts in the commonest variety of syphilis of the stomach, which arises as a submucous gumma. A particularly interesting point was the discovery of abundant spirochaetes in an actively developing part of the lesion.

2. Cases of this kind resemble so closely carcinoma of the stomach that an erroneous diagnosis, in the absence of other overt signs or a history of syphilis, is very likely to be made.

3. The resemblances to carcinoma include:

(*a*) The invariable presence of a palpable tumour in the epigastrium.

(*b*) The occurrence of loss of weight and cachexia.

(*c*) The absence of free hydrochloric acid in the gastric juice.

4. Perforation of the gummatous ulcer may lead to fatal peritonitis.

5. Haematemesis may occur from necrosis of part of the gummatous mass, before endarteritis and thrombosis of the arteries have occurred.

6. The pathological lesion consists essentially of the development of a granulation tissue mass, or gumma, in the submucous layer of the stomach, which soon leads to destruction of the overlying mucosa and to ulceration.

7. The lesion may be seen at various stages, the centre of the ulcer being almost healed and transformed into scar tissue, while other parts, notably the raised margins, show the active stage of granulation tissue formation. The larger blood-vessels in the obsolete central parts of the ulcer show well-developed endarteritis obliterans, but in the zone of active growth these changes are absent.

8. From a brief historical survey of the literature it is evident that the prognosis in such gummatous lesions of the stomach is good when antisyphilitic treatment is employed. The literature also shows that this is the most frequent form of an uncommon variety of visceral syphilis. Many more descriptions of the condition have been found on record than the scanty references to the subject in British text-books might be taken to indicate.

Other varieties of gastric syphilis must at present be regarded as of extreme rarity, although it may be pointed out that little is known of the effects of early syphilis on the structure of the stomach.

The writer wishes to thank Dr. Sidney Martin for permission to publish this case.

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DESCRIPTION OF PLATES.

PLATE 8. FIG. 1. Photograph of the specimen of syphilis of the stomach. A. Oesophagus. B. Pylorus. C. In tissue from an area similar to this abundant spirochaetes were found. D. Two perforations of the ulcer.

PLATE 9, FIG. 2. Microphotograph of a section showing the character of the spirochaetes. Stained by Levaditi's method. ($\frac{1}{12}$" oil-immersion lens, No. 4 eyepiece.)

FIG. 3. Microphotograph of a small artery in the floor of the ulcer, showing endarteritis obliterans. Haemalum and eosin (× 50).

FIG. 4. Microphotograph of a moderately active part of the ulcer, showing the granulation tissue. Part of the muscular coat of the stomach is seen below. Haemalum and eosin (× 50).

FIG. 5. Microphotograph of the mucosa of the stomach in a part not involved by the ulcer. The changes are those of interstitial gastritis, and the muscularis mucosae remains intact. Haemalum and eosin (× 50).

FIG. 1

FIG. 2

FIG. 3

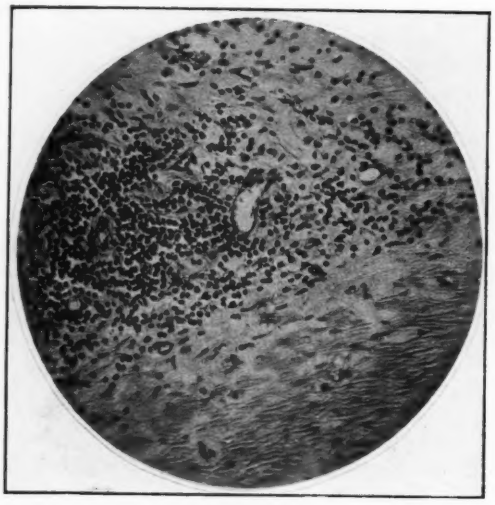

FIG. 4

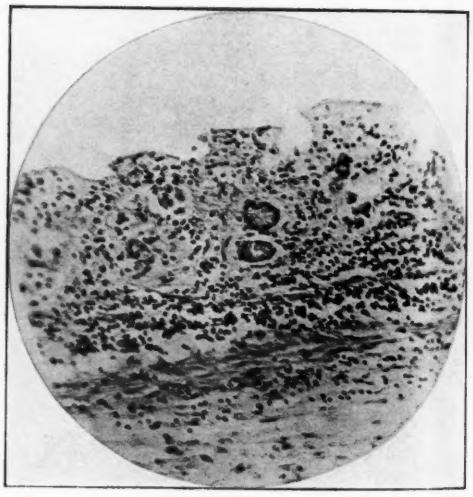

FIG. 5

THE EXCRETION OF POTASSIUM IODIDE IN THE URINE IN HEALTH AND DISEASE: ITS USE AS A TEST OF RENAL FUNCTION

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THE objects of this paper were:

I. To establish the normal quantitative excretion of potassium iodide in the urine after a single dose;

II. To investigate the effect upon this excretion of various diseases, especially diseases of the kidneys; and

III. To consider whether the variation in the iodide excretion might be of value as a test of renal function.

Previous Work on the Excretion of Iodide and its Use as a Test of Renal Function.

Potassium iodide was used formerly by Dyce Duckworth and other workers, and more recently it was reintroduced by Schlayer as a renal function test in cases of nephritis. His work was founded on animal experiments and observations on men, and his conclusions were of considerable interest.

To men (1) he gave a single dose of 0·5 grm. of potassium iodide, and the urine was tested every two hours for the presence of iodide, the time during which it was excreted being noted. This time did not in normal persons exceed sixty hours. If iodide was present after that time he concluded that there was renal inefficiency.

His early work (2) with animal experiments led him to believe that cases of acute toxic nephritis could be divided into two categories which he termed vascular and tubular; the vascular type corresponded to the glomerulo-nephritis of the usual terminology and had no relation to the arterio-sclerotic kidney. The vascular type was described as starting in the glomeruli and leading to the complete cessation of water output; the histological changes were very small; such a condition resulted from the administration of arsenic and cantharides. The tubular type commenced in the tubules, the glomeruli being unaffected and the water output remaining normal in the presence of severe anatomical changes:

secondary destruction of the glomeruli might occur but was not so advanced as in the vascular type: such lesions were caused by chromates and sublimate.

From observations on men he concluded that acute nephritis with scanty urine corresponded to the vascular type which he had described in animals: in these cases he found that lactose, his other test substance, was delayed, that chloride was not retained, and that iodide was not affected. He observed that many damaged kidneys passed an excess of water, the glomeruli having become over-sensitive. Scanty urine he therefore considered a sure sign of severe damage, but damage might exist with a normal or an increased quantity of urine. The specific gravity depended on the chloride excretion and therefore on the efficiency of the tubules.

In animals he found that the iodide excretion was very constant. The volume of urine was found to have no effect on the iodide excretion in rabbits. Heffter (3) found that this was true in men; his observations were made on beer-drinkers. Schlayer quoted certain cases of ascites and fresh pleural effusion in which there was retention of fluid but not of iodide. From his animal observations he claimed that iodide and chloride were both excreted by the tubules, but that the excretion of each was independent of the other. Chloride might be retained by extra-renal conditions, such as morbus cordis, but the iodide was not affected: the same was true when the chloride excretion rose above normal. Theocin and diuretin easily influenced the excretion of chloride but not that of iodide.

In a later paper he applied these conclusions to chronic cases (4); he described cases with polyuria and glomerular hypersensitiveness in which a dose of salt caused diuresis, and cases with oliguria and severe damage to the glomeruli.

Herringham and Trevan (5) employed the iodide test in a few cases: they too were particularly interested in the localization of function in the kidney. They found that in five out of their six cases the iodide and the chloride were similarly affected; in the remaining case the iodide excretion was low and the chloride excretion almost normal.

Rowntree found that lactose, iodide, and chloride were all delayed in cardio-renal cases with a moderate degree of passive congestion: he preferred phenol-sulphophthalein to any of them as a test of renal efficiency.

In this investigation iodide was used as a test of general efficiency, and no attempt was made to correlate its excretion with a lesion of any particular structure in the kidney. The results obtained, however, tend to support the conclusion that the function of chloride and iodide excretion is distinct from that of urea excretion.

Method employed in this Investigation.

For purposes of comparison a constant dose of iodide was given and a standard method of estimating the quantity of iodide in the urine employed. For the sake of simplicity a dose of two grm. of potassium iodide was given to all patients in

preference to regulating the dosage by the body weight of the patient. The two-grm. dose was given to children of eight without ill effect: on rare occasions a slight degree of iodism was produced. Further the body weight, especially that of persons with oedema, varies considerably and has little relation to the weight of the tissues actively engaged in the work of metabolism.

A variety of methods for estimating the iodide in the urine were tried; the best appeared to be that of setting the iodine free with fuming nitric acid and extracting it with chloroform, the solution in chloroform being then titrated with centinormal solution of sodium thiosulphate. This method was elaborated and employed in all the cases investigated. The method had previously been used by Dr. Trevan, and I am indebted to him and to Dr. George Graham for much assistance.

The dose of iodide was given in water at six o'clock in the evening. The patient emptied the bladder at this time; the urine passed during the next twelve hours was collected, the last addition being made at six o'clock the following morning, when the bladder was again completely emptied. A second twelve-hourly specimen was similarly collected. The total volume of the specimens was carefully measured, but a sample of 100 c.c. of each was sufficient for the estimation.

Fuming nitric acid was added to 25 c.c. of the urine in order to set free the iodine. A few drops were often sufficient, but some slight experience was necessary to gauge the correct amount; slightly more was required if there was a large amount of albumin present. Excess of acid may cause a further reaction with disappearance of the iodide from the free state, and in all cases excess of acid increased the difficulties of the estimation. Forty c.c. of chloroform, more or less, were then added to extract the iodine: violent shaking was avoided because an emulsion was easily formed which required a long time to separate: about three minutes of gentle agitation were sufficient to extract the iodine. After standing for a minute or two the chloroform solution was separated off. The urine was then extracted with a second smaller quantity of chloroform, and a few more drops of nitric acid were usually added at this stage to make certain that all the iodine was free. The solution of iodine in chloroform was then washed in three changes of distilled water in order to remove all traces of acid, and was titrated with centinormal sodium thiosulphate solution, using starch emulsion as an indicator: the blue colour disappeared quite sharply. The end-point was good, if the acid had been satisfactorily removed.

1 c.c. of the thiosulphate solution equals 0·00166 grm. of potassium iodide. The chloroform was redistilled and used repeatedly.

Accuracy of the Method of Estimation.

In order to test the accuracy of the method of estimation urines were made up by adding to them known quantities of potassium iodide, and these were then estimated. The results obtained fell within 5 per cent. of the actual amount

present, and as the variations to which importance was attached were large the method was considered to be sufficiently accurate for the purpose of this investigation. The following were the figures obtained:

		Error.
Exp. I. 220 c.c. normal urine mixed with 20 c.c. 1% potassium iodine.		
Actual quantity of potassium iodide in 240 c.c.	0·20 grm.	−5%
Estimated „ „ „ „	0·19 grm.	
Exp. II. 160 c.c. normal urine and 20 c.c. 1% potassium iodide.		
Actual quantity of potassium iodide in 180 c.c.	0·20 grm.	+3½%
Estimated „ „ „ „	0·207 grm.	
Exp. III. 195 c.c. albuminous urine and 25 c.c. 1% potassium iodide.		
Actual quantity of potassium iodide in 220 c.c.	0·25 grm.	+3%
Estimated „ „ „ „	0·254 grm.	

The Excretion of Potassium Iodide by Normal Persons.

Iodide was given to four apparently normal individuals in order to observe the normal excretion of iodide in the urine. In the case of one of them (2) the conditions of the experiment were varied so as to observe the effect which the fluid intake had upon the quantity of iodide excreted. Patient No. 2 was given iodide on four occasions which were spread over a period of eighteen months; on the second occasion (5.2.21) his fluid intake was restricted to two ounces in the first twelve hours, and on the third he drank a large excess of water (12.2.21). The result was a considerable variation in the volume of urine passed without any appreciable change in the amount of iodide eliminated. The fourth occasion was one of the hottest days of July, 1921, but again the iodide was not influenced. These results agree with those of Schlayer and Heffler.

From this small number of experiments it appeared that a normal individual excreted 45 per cent. or more of a dose of 2 grm. of potassium iodide in the first twelve hours, and that the exact amount excreted by any individual was constant, with small variations over prolonged periods, and was not affected by the fluid intake or by the volume of urine excreted.

Patient.	Date.	Weight of Potassium Iodide excreted in First Twelve Hours.	Weight of Potassium Iodide excreted in Second Twelve Hours.
1.	3.1.20	0·88 grm. or 44% of dose	0·47 grm.
2.	3.1.20	0·90 grm. or 45% of dose	0·33 grm.
	5.2.21	1·08 grm. or 54% of dose 625 c.c. of urine	0·15 grm.
	12.2.21	1·04 grm. or 52% of dose 1150 c.c. of urine	0·23 grm.
	9.7.21	1·10 grm. or 55% of dose	
3.	26.5.21	0·95 grm. or 47% of dose	0·37 grm.
4.	22.7.21	1·20 grm. or 60% of dose	0·20 grm.

The Excretion of Potassium Iodide in Disease.

In considering the question of the excretion of potassium iodide in disease, and especially in disease of the kidneys, it was necessary to lay down the criteria by which the presence of renal impairment is to be recognized. These criteria fall under three headings.

1. *Clinical.* The clinical signs of renal inadequacy were, if present, more important than anything else: by these alone in many cases a diagnosis of nephritis could confidently be made. The cases fall into two main groups, namely acute nephritis in which there was the possibility of complete clinical recovery, and chronic nephritis in which there was some degree of permanent damage to and impairment of the kidney: both classes had, of course, numerous subdivisions (glomerular, tubular, interstitial, arterio-sclerotic, &c.,) depending on the relative affection of the various structures composing the kidney. Briefly the facts to which importance was attached were:

(*a*) The history of the illness and of any preceding attacks, special note being made of statements in the history pointing to the existence of the symptoms of previous renal inadequacy, such as oedema, haematuria, breathlessness, giddiness, headache, haemorrhages (epistaxis, renal epistaxis, cerebral haemorrhage), disturbances of vision, convulsions.

(*b*) The signs discovered on examination, in particular the changes in the urine (volume, presence of albumin, blood-cells and casts); the presence of oedema with its distribution and degree; the presence of cardio-vascular hypertrophy, otherwise unaccounted for, and of a blood-pressure persistently raised to the region of 180 mm. or more; the presence of albuminuric retinitis and of sclerosis of the retinal vessels; the signs of uraemia, headache, vomiting, epigastric pain, dyspnoea, &c.

2. *Renal function tests.* These tests were employed to confirm and amplify the opinion formed on the clinical findings. In addition to the proposed iodide test three tests were commonly applied to the cases considered in this paper.

(*a*) The estimation of the urea in the blood. The method used comprised the precipitation of the albumin by trichloracetic acid and the direct estimation of the urea bodies by the Ambard hypobromite method. The normal figures were taken as 37 to 50 mg. of these substances estimated as urea in 100 c.c. of blood. Care was taken not to attach undue importance to slight increases (60 mg.) unless such an amount was found to be present on several occasions. In the same way normal figures carried less weight if the patient was taking a diet very poor in nitrogen.

The presence of a high blood urea indicates a high degree of impairment of the renal functions. According to Rose Bradford it is only when less than four-twelfths of the kidney substance remains intact that the blood urea begins to rise above the normal figure: in experiments on dogs he found that if the kidney substance was reduced to three-twelfths the animals died. The blood urea there-

fore is a test of that zone of renal efficiency which lies between four-twelfths and three-twelfths of the normal, and of that zone only.

(*b*) *The urea feeding test.* This was the test recently reintroduced by Maclean. 15 grm. of urea in 100 c.c. of water were given, and the changes in the urea content of the urine passed during the subsequent three hours were studied. In the absence of a marked diuresis a concentration of 2 per cent. in any of the specimens was taken to indicate an efficient kidney: if a marked diuresis occurred, this was taken into consideration in the interpretation of the figures obtained, or else the dose of urea was repeated when the diuresis had passed off. On account of this difficulty it would probably be better to take the actual amount of urea excreted in the various hours as the criterion, 1·5 grm. in any one hour being taken as a normal result in health.

(*c*) The diastase content of the blood and urine. In a few of the cases an estimation of the diastase in the blood and the urine was made. In some cases of nephritis there is a decrease from the normal 20 units in the urine to less than 10 units: this is mainly of value in the differentiation of the toxaemic kidney, e.g. that of eclampsia, in which the diastase in the urine reaches a figure of 100 units or more (Mackenzie Wallis). It is, of course, increased in certain stages of pancreatic disease.

3. *Post-mortem findings.* When the opportunity occurred the findings of the clinical investigation and of the function tests were confirmed at autopsy. Unfortunately the border-line cases in which the tests were of especial interest could not be investigated in this way. The kidneys obtained all showed advanced and general changes, and it was not possible to correlate a failure of any one test with a lesion of any definite structure in the kidney.

Classification of Cases.

Iodide was given to 29 patients in whom it was thought probable that the kidneys might be inefficient. In the worst cases which proved fatal from uraemia it was found that only 5 per cent. or 10 per cent. of the dose was excreted in the first twelve hours, and in one of them none whatever could be detected in the urine. From such extremes all degrees of failure were found until the normal was reached or even exceeded. For purposes of discussion it was found convenient to divide these cases into four groups: in Class A the excretion reached or exceeded 35 per cent., and into this group fell nine of the cases; in Class B the excretion was between 25 per cent. and 35 per cent., and the cases numbered three; in Class C there were nine excreting 15 per cent. to 25 per cent.; and in Class D eight who failed to eliminate 15 per cent.

The defects of this classification were two: 1. Occasionally a patient excreted a small amount of iodide in the first twelve hours, but in the second twelve hours excreted about the same amount as in the first twelve hours. Such cases are best placed in the class above; e.g. a patient who excreted 23 per cent. in the first period and 20 per cent. in the second would be better placed in Class B than

TABLE OF CLASS A. *35 per cent. or more of Iodide eliminated.*

Case No. Age. Length of Illness.	Diagnosis.	General Symptoms.	Oedema.	Cardio-vascular Changes.	Urine.	Blood Urea.	Urea Feeding.	Iodide.	Remarks.
5. 27 yrs. 1 yr. 9 m.	Chronic parenchymatous nephritis	Headache, dyspnoea, bronchitis	Moderate	B. P. 96 : 80	Albumin, blood, hyaline casts	8th day, 73 mg.	24th day, 1·4 % 31st day, 2·0 %	44th day, 37 %	Heart dilated, liver enlarged. Treated with digitalis Diastase : blood 5–10 units. Urine 20 units
6. 24 yrs. 5 m.	? Arterio-sclerosis, heart failure	Headache	Marked	B.P. 196 : 103 9th day 122 : 70	Albumin 0·4 %, falling to a trace	3rd day, 38 mg.	4th day, 1·6 % 14th day, 2·9 %	5th day, 38 %	Discharged improved and without oedema. 4 m. later he was remaining well
7. 18 yrs. 1 m.	Acute nephritis	Headache, vomiting, delirium	Moderate	B. P. 120 : 60	Albumin 0·4 %, blood, granular casts	3rd day, 37 mg. 8th day, 25 mg. 15th day, 47 mg.	—	3rd day, 40 %	Moderately well 8 m. after discharge
8. 42 yrs.	Acute bronchitis, emphysema, arterio-sclerosis	—	Absent	B. P. 180 : 126 Arteries thickened	Albumin a trace, vol. of urine 700 c.c.	—	—	6th day, 70 %	Heart hypertrophied and dilated. Liver enlarged
9. 31 yrs. 3 m.	Retinitis, albuminuria	Headaches, failure of vision	Absent	B. P. 120 : 80	Albumin, vol. of urine 1800 c.c.	2nd day, 28 mg.	4 %	4th day, 36 %	Marked retinitis
10. 69 yrs.	Carcinoma of pancreas	—	Absent	R. P. 140 : 75	Albumin a trace, bile	50 mg.	—	36 %	Urinary diastase 5 units. Kidneys appeared natural at autopsy
11 15 yrs.	Acute nephritis	Adm. as acute pyelitis	Absent	B. P. 130 : 90	Albumin 0·3 %, R.B.C., W. B. C., all casts	6th day, 34 mg. 63rd day, 33 mg.	—	17th day, 39 %	107th day, trace albumin, no R. B. C., no casts. 1 yr. later remaining very well
12. 10 yrs. 3 days	Acute nephritis	Headache, vomiting	Marked	B. P. 105 : 60 12th day 85 : 55	Albumin, blood, granular casts	—	38th day, 1·3 %	40th day, 52 %	Relapsed a few months after discharge
13. 70 yrs. 1 yr.	Arterio-sclerosis	Dyspnoea	Slight	B.P. 165 : 105 Hypertrophy and dilatation of heart	Albumin a trace	—	—	20th day, 47 %	Marked improvement with rest and digitalis

in Class C. Usually the excretion in the second period was considerably smaller than in the first, and fortunately the exceptions were infrequent. An estimation of the iodide in the second period was always made to catch these exceptions. 2. The output in acute or recent cases was dependent on the time which had elapsed since the onset of the disease. Although in no instance were ill effects observed from the administration of iodide, yet we hesitate to give it to patients with acute nephritis in the early stages.

For the sake of clearness the cases are presented in tabular form. A few points require explanation. The diagnoses given are those which are arrived at by the physicians in charge of the cases. The actual dates of the various observations have been omitted, and instead the time is given in the number of days, weeks, or months, counted from the day of first admission to hospital; 'm' stands for months. Similarly the length of the illness given in the first column is given in days, &c., counting back from the day of admission.

Class A. Into this class fell three cases of acute nephritis, three of arterio-sclerosis, one of retinitis and albuminuria, one of carcinoma of the pancreas, and one of parenchymatous nephritis.

In the cases of acute nephritis (Nos. 7, 11, 12) the iodide test was applied one month, two weeks, and six weeks respectively after the commencement of the illness: time had therefore elapsed to allow of some recovery of the renal functions: No. 7 was, however, still suffering from severe uraemic symptoms and from oedema. These patients had no retention of urea, but No. 12 gave a poor response to urea feeding, 1·3 per cent.: this patient did not recover as completely as the other two, so that in this case the urea test gave a more accurate prognosis than did the iodide test. All these patients were discharged from hospital with little or no albuminuria, no red blood-cells in the urine, and without appreciable cardio-vascular changes. Nos. 7 and 11 have remained well for over eighteen months, and No. 12 relapsed.

Patients Nos. 6, 8, and 13, who were diagnosed as arterio-sclerosis, excreted respectively 38 per cent., 70 per cent., and 47 per cent. of their iodide. No. 6 was a young man with cardiac failure in whom a condition of chronic nephritis was suspected: the blood urea was 38 mg., and by urea feeding a concentration of 1·9 per cent. was obtained on one occasion and 2·9 per cent. on another ten days later. These facts together with the result of rest on the oedema, blood-pressure, and albuminuria caused a good prognosis to be given and the suggestion of nephritis to be withdrawn. Three months later he was seen again and found to present no symptoms or signs of disease. No. 8 came in with acute bronchitis and emphysema: she had a trace of albumin in her urine, which was of normal specific gravity, and her blood-pressure was high and her arteries thickened: she was an unsuitable patient for a prolonged stay in hospital and was not further investigated. No. 13 was an old man who complained of breathlessness and had oedema of cardiac distribution.

Patient No. 5 was diagnosed as parenchymatous nephritis and heart failure. The evidence for the existence of nephritis was the distribution of the oedema,

TABLE OF CLASS B. *25 per cent. to 35 per cent. of Iodide eliminated.*

Case No. Age. Length of History.	Diagnosis.	General Symptoms.	Oedema.	Cardio-vascular Changes.	Urine.	Blood Urea.	Urea Feeding.	Iodide.	Remarks.
14. 22 yrs. 3yrs.	Chronic mixed nephritis	Debility, haematuria	Slight and occasional	B. P. 157 : 70 7th day 128 : 80	2–3 litres daily, albumin. Blood: constant traces	2nd day, 70 mg. 26th day, 40 mg., on low nitrogen diet	—	3rd day, 30 % 14th day, 25 %	Discharged with little improvement. Lost sight of subsequently
15. 50 yrs. 3 weeks	Acute nephritis	Dyspnoea, bronchitis	Marked, absent after 3 m.	B.P. 180 : 100 14th day 190 : 120 82nd day 130 : 90 100th day 124 : 90	Albumin, blood, hyaline and granular casts	6th day, 110 mg. 13th day, 110 mg. 73rd day, 88 mg. 113th day, 77 mg.	—	8th day, 28 % 45th day, 56 %	Slight retinal changes Haematuria persisted till discharge 14 m. later: at work; B.P. 136 : 90; urine contained pus, red cells, granular and epithelial casts
16. 29 yrs. 5 yrs.	Chronic mixed nephritis	Dyspnoea, headache	Moderate	B. P. 170 60th day 140 : 90	Albumin 0·2% to 1·0 %	9th day, 35 mg.	76th day, 3·2 %	12th day, 26 % 47th day, 30·5 % 105th day, 60 %	7 m. after admission she was 'very well'

the urinary changes, and the results of the function tests. The blood urea was increased to 78 mg., and urea feeding gave concentrations of 1·4 per cent. and later 2·0 per cent. The evidence was somewhat slender, although a raised blood urea was taken by Rose Bradford as indicating destruction of more than eight-twelfths of the kidney tissue.

Patient No. 10 suffered from carcinoma of the pancreas. Since her urinary diastase was only 5 units, it was suggested that she might have defective kidneys, but no evidence of this was found in the symptoms or in the blood urea and iodide estimations: *post mortem* the kidneys showed no macroscopic disease, but this was not confirmed microscopically.

Patient No. 9 came to the hospital complaining of defective vision, and on examination retinitis and albuminuria were found. No other clinical evidence of the presence of nephritis was found and the urea tests likewise failed to indicate it. Nearly two years later he was attending the Western Ophthalmic Hospital and the retinal condition had advanced.

Class B. In this class there were three cases of nephritis, two chronic and one acute. Possibly two of the cases of acute nephritis in Class A (Nos. 8 and 12) would have fallen into this category if the test had been applied earlier.

Patient No. 15 had acute nephritis at the age of 50. He had worked until the day of admission to hospital. His progress was very slow: the oedema persisted for three months; the blood urea fell slowly from 110 mg. on admission to 77 mg. four months later. He had persistent haematuria and a few red cells were still present in the urine on his discharge from hospital. The iodide excretion had returned to normal by the middle of the second month. Twelve months later he still had albumin, blood, granular and epithelial casts in his urine, but was doing his work as a bookbinder's cutter without losing time: no cardio-vascular changes could be detected and the oedema had not recurred.

Patient No. 14 was a pensioner with a chronic nephritis following trench nephritis which he had contracted two years previously. He made very little progress while in hospital and has been lost sight of since. No. 16 had a five years' history of oedema, headache, and dyspnoea: her age was 29 years: her symptoms were relieved after a stay of a month in hospital, but the iodide excretion did not recover for another two months, and she was kept in bed on that account. The blood urea and the urea feeding test did not in this case indicate the necessity for prolonged rest. Three months after her discharge from hospital she was very well, although there had been a temporary return of the oedema of the legs.

Class C. With one exception (Patient No. 20) a definite clinical diagnosis of nephritis was made in all these cases. Patient No. 20 excreted 22 per cent. of the iodide in the first twelve hours and 20 per cent. in the second twelve hours, so that the iodide test gave a somewhat uncertain reading: in all the other cases in this group the excretion for the second twelve hours was much smaller than that for the first. Albumin was found in the urine of this patient in the course of a routine examination, and she was admitted to hospital for investigation: with the exception of the discovery of granular casts in her urine no other evidence of

nephritis was forthcoming. A tentative diagnosis of chronic parenchymatous nephritis was made, but on re-examination a year later there had been no further developments.

The diagnosis of nephritis in the case of Patient No. 19 presented a little difficulty: it rested upon the presence of a trace of albumin and an isolated blood urea estimation of 70 mg.: to confirm the diagnosis the patient was seen again after ten months, and was found still to have a blood urea of 68 mg.: he was therefore considered to have a definite nephritis.

Patients Nos. 23 and 25 were cases of acute nephritis. The low iodide figure in No. 23 was obtained early in the course of the disease; it is possible that other cases of acute nephritis would have been in this category if the test had been applied earlier. No. 23 was kept in hospital for a prolonged period after her symptoms had disappeared and the urea tests had become normal: this was done largely because her power of excreting iodide recovered so slowly, the only clinical sign of incomplete recovery being the persistence of a few red cells in the urine.

In No. 24 the iodide gave an indication for prolonged treatment, and traced the slow progress of recovery. The result of the urea feeding test was abnormally low on the tenth and sixteenth days; on the twenty-ninth day, although the concentration was but 1·5 per cent., the volume of urine excreted in the hour was 127 c.c. and the amount of urea 1·9 grm.: such figures I consider indicate renal efficiency. But when the nitrogenous elements in the diet were increased urea retention occurred and the blood urea rose to 65 mg. per cent. The iodide was still definitely abnormal on the thirty-ninth day and had not completely recovered on the seventy-ninth day.

Patient No. 21 was of interest on account of the failure of the urea feeding test in spite of a very definite and advanced condition of nephritis. The diastase test showed the presence of 4 units, and the blood urea was 75 mg. just after admission. The iodide proved to be reliable, showing an excretion reduced to 17·5 per cent.

The mechanism of urea excretion of Patient No. 18 was little disturbed in spite of a severe nephritis. An early urea feed gave a concentration of less than 2 per cent. but later it rose above that figure. He was one of the first patients investigated by means of the iodide test, and he had been in hospital for two months before this test was applied: it gave a normal result after four months, and it was not until that time that the oedema began definitely to disappear. He went to a convalescent home after five months and then had slight oedema; he returned after two months in a much improved condition and without oedema. Since then he has been at work as a signal fitter on a railway without loss of time through ill health. He came to the hospital again after seventeen months and was then looking and feeling perfectly fit: there was no cardiac hypertrophy and the blood-pressure was 120: 90 mm.: he excreted 36 per cent. of his iodide and the specimen of urine tested contained no albumin.

Class D. There could be no doubt from the clinical pictures that a severe

TABLE OF CLASS C. *15 per cent. to 25 per cent. of Iodide eliminated.*

Case No. Age. Length of Illness.	Diagnosis.	General Symptoms.	Oedema.	Cardio-vascular Changes.	Urine.	Blood Urea.	Urea Feeding.	Iodide.	Remarks.
17. 30 yrs. 4 yrs.	Chronic mixed nephritis	Headache, vomiting	Always absent	B. P. 220	Albumin 0·6 %, hyaline and granular casts, vol. 2000 c.c.	80 mg.	—	21st day, 22 % 43rd day, 18 %	Slight retinal exudate. Died outside hospital 14 m. later
18. 38 yrs. 5 days	Acute tubular nephritis	'Dizziness'	Marked, and persistent	B. P. 110 : 90	Albumin 1·2 %, hyaline casts	24th day, 34 mg.	2 %	68th day, 24 % 122nd day, 46 % 1 yr. 10 m., 36 %	1 yr. 8 m. later he was very well, working as signal fitter. No oedema. B. P. 120 : 90
19. 44 yrs. 1–2 yrs.	Chronic myocarditis, arterio-sclerosis, chronic nephritis	Dyspnoea, syncopal attacks	Slight ascites	Slight hypertrophy and dilatation, B. P. 130 : 95	Albumin a trace	17th day, 70 mg. 10th m., 68 mg.	2 %	30th day, 18·5 %	9 m. later well, no fainting attacks, dyspnoea, B. P. 128 : 90. Marked emphysema
20. 19 yrs. ?	Albuminuria, ? chronic parenchymatous nephritis	'Nerves'	Absent	B. P. 113 : 82	Albumin 0·3 %, granular casts	27 mg.	—	15th day, 22 % 20 % in 2nd twelve hours	Came to hospital complaining of nerves. Albumin found in routine examination. 11 m. later no symptoms had developed
21. 40 yrs. 5 yrs.	Chronic mixed nephritis	Headache, vomiting	Marked	Hypertrophy, B. P. 160 : 90	Albumin 0·2 %	2nd day, 75 mg. 27th day, 35 mg. (low protein diet)	10th day, 2·5 %	3rd day, 17·5 %	Diastase 4 units

22. 20 yrs. 3 yrs.	Chronic parenchymatous nephritis	Headache, slight dyspnoea	Marked	B. P. 142 35th day 170 : 130 70th day 160 : 120	Albumin 0·2 %	8th day, 40 mg. 47th day, 50 mg. 69th day, 68 mg.	—	3rd day, 21 % 15th day, 21 % 21 % in 2nd twelve hours	16 m. later she was an inpatient in the German Hospital (nephritis)
23. 15 yrs. 2 weeks	Acute nephritis	Pallor	Marked	B. P. 172 : 90 6th day 105 : 80 120th day 112 : 80	Albumin 0·05 to 0·25 %. Blood, granular and hyaline casts	3rd day. 56 mg. 7th day, 63 mg. 25th day, 43 mg. 40th day, 42 mg.	92nd day, 1·98 % in 3rd hour	3rd day, 15 % 31st day, 28 % 149th day, 49 %	Attack was preceded by cervical adenitis. Persistent haematuria. Diastase 3 units. After 10 m., pallid, occasional oedema. B. P. 126 : 85. Urine, 0·1 %. Albumin, four red cells
24. 25 yrs. 6 m.	Chronic parenchymatous nephritis	Recurrent oedema	Slight, absent by 7th day	B. P. 165 : 105	Albumin 1 %, hyaline and granular casts	3rd day, 40 mg. 29th day, 82 mg., after urea feeding 81st day, 65 mg.	10th day, 1·2 % 16th day, 1·2 % 29th day, 1·5 %	2nd day, 22 % 39th day, 18 % 79th day, 28 % 20 % in 2nd twelve hours	Discharged after 110th day free from symptoms, no red cells in urine, no oedema : hyaline and granular casts still present A month later, remaining well. B. P. 175 : 125
25. 12 yrs. 14 days	Acute nephritis	Headache, vomiting	Marked, persisted for 5 m.	B. P. 140 : 90 14th day 114 : 70 6th m. 114 : 82	Albumin, blood, epithelial and granular casts	4th day, 105 mg. 7th day, 160 mg. 21st day, 145 mg. 32nd day, 100 mg. 60th day, 50 mg.	71st day, 1 53 % 154th day, 2·3 %	27th day, 23·5 % 61st day, 32 % 171st day, 65 %	Blood cells were constantly present for 4 m. B. P. 169th day, 114 : 82. Case still in hospital

degree of nephritis was present in all the cases of this group. Five patients died in hospital and the diagnosis was confirmed at the autopsy.

The kidneys of Patient No. 26 weighed 7½ and 8 oz.: there were areas of round-celled infiltration and fibrosis in the cortex, and in these areas the Malpighian bodies had undergone complete hyaline degeneration; the Malpighian bodies elsewhere showed proliferation of the epithelium and the tubules showed granular and fatty degeneration. There were slight arterio-sclerotic changes. In No. 27 the kidneys presented marked interstitial changes: all the glomeruli were affected, some showed swelling and fatty changes and some were completely degenerate: there was widespread fatty degeneration of the tubular epithelium, which in many parts had disappeared: even the comparatively healthy glomeruli were surrounded by fibrous tissue. The kidneys of No. 28 showed thickening of the capsular epithelium and increase of the nuclei in the glomeruli: there was cloudy swelling of the tubular epithelium and several areas of interstitial infiltration and fibrosis. In No. 31 most of the glomeruli were obliterated by concentric fibrous proliferation or showed complete hyaline degeneration. There were marked interstitial changes. In No. 32 there was a marked increase of the epithelium of the capsules and development of fibrous tissue; complete amyloid degeneration had occurred in other glomeruli: the tubules were compressed in some parts and dilated in others, and contained albuminous exudate. The kidneys together weighed 8 oz.

Patient No. 29 was sent from the hospital to a convalescent home, and had then slightly improved; he had become definitely worse before leaving the home, but was subsequently lost sight of. Patient No. 30 was alive seven months after discharge, but her condition was steadily becoming worse. No. 33 was suffering from chronic nephritis and heart failure: she also failed to improve, for the blood urea rose from 75 mg. at the time of admission to over 100 mg. six weeks later, and her attacks of uraemic dyspnoea increased in severity.

Results of the Investigation in Disease.

From the foregoing it appeared that an excretion of 35 per cent. or more of the dose of iodide in the first twelve hours occurred in all patients without nephritis with the possible exception of the doubtful case, No. 20. A similar figure was obtained in some cases of acute nephritis, sometimes at an early stage of the disease, and also in one mild case of parenchymatous nephritis.

All the patients who excreted less than 35 per cent. had nephritis of some degree, and, except in acute nephritis, an excretion of less than 25 per cent. did not occur unless there was a condition of advanced chronic nephritis. These last patients did not improve in their power of iodide elimination or in their clinical condition to any appreciable extent.

Patients excreting less than 15 per cent. were all very advanced in their disease, and the prognosis was extremely bad in all of them.

It is therefore claimed that when the iodide excretion falls below 35 per cent. the test is a reliable sign of renal damage. An excretion of more than 35 per

Case No. Age. Length of Illness.	Diagnosis.	General Symptoms.	Oedema.	Cardio-vascular Changes.	Urine.	Blood Urea.	Urea Feeding.	Iodide.	Remarks.
26. 41 yrs. 1 m.	Chronic parenchymatous nephritis	Headache, dyspnoea	Slight, persistently increasing	B. P. 180 : 96	Albumin 0·9 %, blood and granular casts	16th day, 105 mg. 30th day, 120 mg. 44th day, 300 mg. 68th day, 200 mg.	—	9th day, 13 % 48th day, nil	Death on 82nd day. Autopsy showed: (i) Chronic parenchymatous nephritis with early chronic interstitial nephritis (ii) Ulcerative endocarditis
27. 56 yrs. 6 m.	Chronic interstitial nephritis	Dyspnoea	Present, slight	Hypertrophy B. P. 250:160 29th day 150 : 85	Albumin	2nd day, 130 mg.	—	2nd day, 4·5 %	Retinitis. 30th day, death with acute uraemia
28. 28 yrs. 2 yrs.	Chronic parenchymatous nephritis	Dyspnoea	Marked	Aortic regurgitation B. P. 160 : 40	Albumin 0·4 %, trace blood, granular casts	3rd day 94 mg. 7th day, 140 mg.	—	7th day, 12·5 %	16th day, purpura. 17th day, faucial diphtheria. 20th day, death. Autopsy showed: (i) Diphtheria (ii) Infective endocarditis (iii) Chronic parenchymatous nephritis
29. 34 yrs. 2 yrs.	Chronic mixed nephritis	Headache, vomiting, polyuria	Absent	Hypertrophy B. P. 250:160 3rd day 180 : 145	Albumin 1·5 %, blood, hyaline casts	154 mg. 7th day, 110 mg.	—	5th day, 7·5 %	Retinitis
30. 47 yrs. 6 m.	Chronic diffuse nephritis	Headache, dyspnoea	Moderate	Hypertrophy B. P. 180 : 95 44th day 150 : 90	Albumin 0·5 %	1st day, 56 mg.	35th day, 1·65 %	8th day, 8 %	Retinitis. Discharged after 2 m. During next 7 m. steadily deteriorated
31. 27 yrs. 1 yr.	Chronic mixed nephritis	Asthma	Moderate before admission	Hypertrophy B. P. 140 : 85	Albumin 0·1 %, few red cells, granular casts	9th day. 356 mg. 38th day, 350 mg.	—	38th day, 2·4 %	Death on 43rd day
32. 46 yrs. 2 m.	Chronic interstitial nephritis	Headache, dyspnoea	Marked pleural and peritoneal effusion	Hypertrophy B. P. 236 : 128	Albumin 0·4 %, blood, hyaline and granular casts	5th day, 435 mg.	—	2nd day, 3·7 %	Retinitis. Death on 10th day, with chronic uraemia. Autopsy showed chronic interstitial nephritis, and cardiac hypertrophy (22 oz.), haemopericardium, hydrothorax
33. 59 yrs. 2 yrs.	Chronic interstitial nephritis, cardiac failure	Dyspnoea, orthopnoea, asthma	Marked pleural and peritoneal effusion	Hypertrophy and dilatation B. P. 182 : 142 6th day 195 : 128	Albumin 0·4 %, blood casts	75 mg. 22nd day, 85 mg. 51st day, 103 mg.	—	5th day, 7·5 %	Diastase 50–100 units. Little improvement while in hospital: recommended for infirmary

cent. does not exclude nephritis, for such an amount was excreted in some active cases in the later stages of acute nephritis when resolution might have occurred, and in cases of chronic nephritis after prolonged treatment when functional recovery had occurred, although the structural damage remained.

Recovery of the ability to excrete iodide was observed in many of the cases, both acute and chronic, to which the test was applied more than once: this recovery appears to be a reliable basis for a favourable prognosis (cf. Nos. 15, 16, 18, and 23). Usually the iodide excretion recovered more slowly than the urea excretion, but the reverse was true in Case 15: in this patient the blood urea remained persistently raised although the iodide recovered.

The Value of the Iodide Excretion as a Test of Renal Function.

It is easy to multiply the tests of renal function, but our aim should be to use as few of them as possible and to gain from these the maximum of information. A new test must therefore, in addition to being reliable, give fresh information of use in diagnosis, prognosis, or treatment.

From consideration of Cases 16, 18, 19, 21 it is apparent that the iodide test might well be of use in diagnosis. In Cases 16, 18, and 21, although there could be no doubt clinically that there was a definite nephritis, yet the more usual tests of renal function did not give such definite readings as might have been expected. It seems clear that the iodide tests a different part of the kidney than that which is tested by the urea tests, but no evidence was obtained in this work which would aid in the location of either function in any particular structure in the kidney.

However, the iodide test is of greater value in prognosis. The cases have been classified according to their iodide output, but had they been arranged according to their prognoses as arrived at on other grounds they would have fallen approximately into the same categories. The patients who excreted less than 15 per cent. (Class D) had the clinical signs of severe renal damage; they showed no tendency to improvement, most of them steadily deteriorating and terminating fatally in a few months. In the group of patients who excreted 15 per cent. to 25 per cent. of the iodide there were two types of cases: those in whom the power of excretion did not recover and whose subsequent progress was unfavourable (Nos. 17 and 22); and those in whom the iodide excretion did recover and whose progress was good (Nos. 18, 23, and 25). All these last cases were cases of acute nephritis. Of those who excreted 25 per cent. to 35 per cent. two recovered the power of iodide elimination, and of these, one (No. 16) progressed well, and one (No. 15) moderately well considering the unfavourable environment to which she returned; the one who failed to improve his iodide excretion showed practically no amelioration of his symptoms even while under treatment in hospital. The improvement of the iodide output is a valuable sign of recovery. The prognosis of the patients who excreted more than 35 per cent. was good as far as their renal condition was concerned, but unimpaired power of iodide elimination is of less significance than its impairment.

The iodide test was of value in treatment particularly in Nos. 16, 23, and 26: in these patients the iodide excretion improved slowly but surely under treatment, and this improvement continued after the clinical condition had become satisfactory, and after the urea tests had ceased to indicate any renal damage. The treatment of these patients was prolonged very largely on account of the slow recovery of the iodide output, and when on clinical grounds they appeared to be stationary the iodide test proved itself a useful index to the progress of recovery. In these cases the iodide test was of considerable value.

The obvious advantage of employing an extraneous substance as a test was demonstrated in Patient No. 24. The blood urea in this case varied with the quantity of protein in the diet. The iodide test traced the progress without the necessity of restricting or analysing the diet.

Conclusions.

1. The iodide test is a reliable indication of nephritis when the excretion falls below 35 per cent.

2. In certain cases of nephritis it is the only test of function which shows that there is renal damage.

3. It is a sign of good prognosis in nephritis when the excretion remains unimpaired throughout; of fair prognosis when it recovers after being impaired, especially if this occurs after a short space of time; and of bad prognosis and of advanced structural damage when it remains indefinitely in the region of 25 per cent. A reduction of the output to 15 per cent. or less is a sign of very advanced progressive disease, and often foretells an early death.

4. In certain cases it may be an aid in treatment, indicating a less advanced stage of recovery than can be recognized by the clinical signs and other function tests.

5. In a few cases there was a slight degree of iodism, but in no case was there any sign of deleterious effect on the kidneys, such as return of haematuria, casts, or oedema.

In conclusion I wish to express my thanks to all those who have assisted me, and particularly to Sir Archibald Garrod, who suggested the problem to me; to Professor F. R. Fraser and Dr. George Graham, who have given me their valuable assistance and advice throughout; and to Dr. Spilsbury and Dr. Geoffrey Evans for the loan of their sections. The collection of the specimens added to the duties of the Sisters and nurses of the Medical Clinic at St. Bartholomew's, and I am grateful to them for their assistance in this important matter.

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RESEARCHES ON THE COMPLEMENT FIXATION REACTION IN HYDATID DISEASE

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Hydatid disease is still commonly met with in the southern states of Australia. During the past ten years there has been no decrease in the yearly incidence of cases admitted to the Melbourne Hospital. Despite modern advances in X-ray diagnosis and improved surgical technique it remains a disease with a high mortality. The medical registrar of this hospital, Dr. K. D. Fairley, has recently analysed the in-patient admissions for the last decade. These figures show that 46 out of 260 cases, or 17·7 per cent., died as a result of this infestation. The majority of these patients were operated on, and of these 28 died subsequently to surgical intervention. Eighteen deaths occurred in hydatid cases which had not been treated by operation. An analysis of the causes of the high mortality rate revealed that earlier and more accurate diagnosis followed by appropriate treatment would have saved the lives of many of these patients. The great difficulty experienced by the clinician in making a diagnosis in echinococcosis is emphasized. Thus, out of 182 patients suffering from echinococcal cysts, the case histories indicated that in only 84 cases, or in 40·7 per cent., had a correct diagnosis been made prior to operation. These figures, which comprise the only large Australian series available since the introduction of routine X-ray examination, forcibly illustrate the limitations of clinical diagnosis if unaided by modern laboratory investigations. In infra-diaphragmatic cysts the X-ray attains its maximum usefulness in localizing rather than in diagnosing echinococcal infestations.

It is the contention of the writer that if the clinician will appeal more often for laboratory assistance, a much higher percentage of cases of echinococcosis will be diagnosed prior to operation and at an earlier stage of the disease. Cases will in consequence receive surgical treatment at a more appropriate time and the mortality rate will be correspondingly lowered.

The Complement Fixation Reaction in Hydatid Disease.

Ghedini (1907) (1) first applied the principles of the Bordet-Gengou method of serological diagnosis to three cases of hepatic hydatid, and also investigated

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ankylostoma, ascaris, and certain taenia infestations from this view-point. Weinberg and Parvu (1908) (2) instituted a series of observations along similar lines on various helminthic infestations in animals, including hydatid of sheep. Weinberg and Vieillard (1909) (3) also obtained positive results in the hydatid of the camel.

In the same year Weinberg (1909) (4) investigated in some detail the value of the serological reaction in human echinococcosis and published several papers on various aspects of this subject. Jianu (1909) (5), in Germany, recorded his results at this period. Israel (1910) (6) and Henius (1911) (7) also reported favourably on specific reactions in hydatid, utilizing aqueous and alcoholic extracts of cyst fluid or both. Other writers reported in similar fashion on the value of the reaction in clinical diagnosis. Weinberg's article in Kolle and Wassermann's *Handbuch* (1913) (8) gives the most complete account of the serological reaction at present available, and includes statistics by different observers collected between 1906–12 and comprising a series of 306 cases. Of these, 251 were positive (82 per cent.), 8 were slightly positive, and 47 were negative. Weinberg, in his total of 60 cases, obtained 46 positive results (76·6 per cent.), while 2 others were slightly positive and 12 were negative.

Zapelloni (1915) (9) found the results quite reliable in his clinic, 93 per cent. of positive reactions having been obtained in a collected series of 500 cases. Controls were always negative.

The Basis of the Reaction.

The complement fixation reaction in echinococcosis is a specific test dependent on the presence of specific antibody in the blood or body fluids of patients who have been absorbing hydatid antigen derived from the cysts of *Taenia echinococcus*. When inactivated serum containing antibody is mixed with hydatid antigen in the presence of complement for one hour at 37° C., the complement is combined in such a fashion that it can no longer be demonstrated in the mixture. If sheep's red blood corpuscles sensitized with a suitable quantity of haemolytic serum (anti-sheep) are then added, and the system is incubated for one further hour at 37° C., no haemolysis occurs, since there is no complement available for this purpose. Absence of haemolysis in such a case indicates a positive reaction. On the other hand, if the serum contains no specific antibody, complement is not fixed in the first stage and is available later to haemolyse the sensitized corpuscles. The presence of haemolysis indicates an absence of antibody and a negative reaction.

The Distribution of Antibody.

The distribution of antibody in the serum and body fluids of patients infested with hydatid is a matter of importance. Lejars (1909) (10) and other observers laid stress upon the fact that antibody, though present in the blood of

cases of hepatic hydatid, was absent from the cerebro-spinal fluid. The validity of these observations in visceral hydatid has been verified in several cases of my series. I have not had the opportunity of investigating the reaction of the cerebro-spinal fluid in hydatid disease of the nervous system, but several different investigators report the presence of antibody in the cerebro-spinal fluid and its absence in the blood under such circumstances. Provided visceral echinococcosis did not coexist, such a finding would almost be anticipated on *a priori* grounds. The clinical importance of these observations is considerable, and the clinician should never remain content with a serological examination of the blood in possible hydatid involvement of the nervous system. The cerebro-spinal fluid itself should always be examined.

In suspected echinococcosis of the lung and peritoneum the investigation of any pleural or ascitic exudate is well worth while. In one case I was able to diagnose the condition from an examination of ascitic fluid alone. The reaction was strongly positive (P. + + +) and the serological diagnosis was subsequently confirmed at operation.

The serological examination in blood collected at autopsy from hydatid cases has proved quite satisfactory in this series.

Technique.

During the past eighteen months I have found the following modification of complement fixation technique of special value in hydatid cases. For purposes of economy of materials small volumes of reagents are measured by Donald's dropping pipettes. Each unit volume of reagent equals 0·1 c.c., and the total volume in the final stage of the reaction is 0·5 c.c. Instead of varying the dilution of serum as advocated by Weinberg, its volume and concentration are kept constant, while the number of units of complement are varied.

Antigen. After a considerable experience with different extracts, I have come to the conclusion that the most readily available and effective antigen consists of hydatid fluid containing scolices collected under sterile conditions from the liver or lung cysts of sheep. The livers and lungs of infested sheep are brought direct from the abattoirs to the laboratory, the wall of the cyst is painted with pure carbolic acid, and a sterile needle with an attached record syringe (10 c.c.) is inserted. The fluid containing scolices is aspirated and stored on ice in sterile test-tubes until required. Before use the fluid is run through a filter-paper, the filtrate being employed as antigen. It is inadvisable to subject the fluid to any unnecessary manipulation, to add antiseptic such as carbolic acid, or to pass it through a candle filter. Such a fluid, provided it is uncontaminated by bacteria and is kept on ice, will preserve its antigenic properties for many weeks. The only other antigen which I have found to yield satisfactory results is prepared by making a saline or alcoholic extract of well-washed scolices. It is not improbable that such extracts will become the standard antigens for future serological work in echinococcosis.

A fresh specimen of 3 per cent. sheep's corpuscles is prepared from sheep especially kept for this purpose by the technique used for the Wassermann test. The corpuscular suspension is sensitized by adding four minimum haemolytic doses of anti-sheep haemolysin and incubating at 37° C. for half an hour. The mixture is then kept in the ice-chest until required.

Blood from the patient. The serum from the patient should be fresh, but satisfactory results are obtained over a period of one week or longer if the specimen has been kept on ice and is uncontaminated.

On the day of the test the serum is diluted with four times its volume of saline (0·85 per cent.) and heated to 55·5° C. for twenty minutes.

Pleural and peritoneal exudates or effusions should be similarly treated. If cerebro-spinal fluid is to be tested it should neither be heated nor diluted, one volume of the pure fluid being used in the reaction.

Complement is obtained from the sera of healthy male guinea-pigs. The serum is allowed to stand in contact with clot for four hours before use. It is then pipetted off and stored on ice until required.

As a routine procedure the minimum haemolytic dose of complement is accurately determined whenever the test is performed. In the final test three, four and a half, and six minimum haemolytic doses are employed.

It is important to note that guinea-pig's serum is never hypersensitive to *clear odourless hydatid fluid.* In a large series of routine observations I have never observed such a fluid displaying anti-complementary tendency. In equal volumes clear hydatid fluid actually fixes less complement than physiological saline, yet it never shows haemolytic tendency. Schilling (1904) (11) showed that cyst fluid was isotonic with the blood of the host. In view of these findings, I no longer regard the titration of this antigen as necessary in routine tests. On the other hand, *turbid* hydatid fluids are often anti-complementary, and should never be used. The turbidity may be dependent on degenerative changes in the cyst or on microbic contamination.

The titre of anti-sheep haemolysin need only be determined at three-monthly intervals. Provided it is stored on ice, there is little depreciation in titre during the first nine months.

Arrangement of the System for the Final Test.

Racks containing four rows of tubes are utilized and the various reagents are added as indicated in the table on p. 248. The quantity of undiluted hydatid fluid employed was 0·1 c.c., but recently I have increased this amount to 0·15 c.c. However, as sufficient time has not elapsed to estimate the validity of this procedure, the original quantity is advocated for routine work.

These reagents are placed in the incubator for one hour at 37° C., and then one volume (i.e. 0·1 c c.) of sensitized sheep's cells are added. The total volume in each tube is then 0·5 c.c. Controls are always employed. Several negative sera, and a known positive hydatid serum, are included in the series of bloods to

be tested. Row IV serves to detect any anti-complementary tendency in each serum under examination. In addition, a complement control (i. e. a tube containing 0·1 c.c. complement and 0·3 c.c. saline) and an antigen control (i. e. a tube containing 0·2 c.c. antigen, 0·1 c.c. of complement, and 0·1 c.c. saline) are set up.

TABLE.

Arrangements of Reagents in the Final Test.

Reagents.	Row I.	Row II.	Row III.	Row IV.
1. Antigen (pure hydatid fluid)	0·1 cc.	0·1 cc.	0·1 cc.	—
2. Patient's serum (diluted 1 in 5)	0·1 cc.	0·1 cc.	0·1 cc.	0·1 cc.
3. Complement (0·1 cc. = 3 minimum haemolytic doses)	0·1 cc.	0·15 cc.	0·2 cc.	0·1 cc.
4. Saline (0·85 %)	0·1 cc.	0·05 cc.	—	0·1 cc.

Readings are made when all the special controls, including the control negative sera, have haemolysed, provided Row IV is clear. Generally the final readings are made within thirty minutes of the addition of the sensitized corpuscles.

Interpretation of Results.

Five different types of reaction are reported to the clinician. A positive + + + reaction means an absence of haemolysis in tubes of Rows I, II, and III, and indicates that at least 6 minimum haemolytic doses of complement have been fixed by the patient's serum. A positive + + means that there is no haemolysis in tubes of Rows I and II, and demonstrates that 4½ units of complement were absorbed. A positive + reaction indicates an absence of haemolysis in the tube of Row I with the fixation of 3 units of complement. All these positive types of reaction are to be regarded as definitely diagnostic of active echinococcal infestation in the host. Where the first tube in Row I shows partial haemolysis only, the reaction is reinvestigated at a subsequent date (P. ±). Complete haemolysis in all three tubes constitutes a negative result, and though such a finding does not exclude the possibility of hydatid, it demands a careful revision of the clinical features of the case where hydatid has been provisionally diagnosed.

The Site and Mode of Production of Hydatid Antigen, with Observations on the Antigenic Value of different Fluids and Extracts used in Serological Work.

There exists a lack of uniformity in opinion regarding the antigenic value of different fluids and extracts employed in the complement fixation reaction for the diagnosis of echinococcosis. Furthermore, as far as I am aware, no investigations have been made concerning the mode of origin or the site of production of hydatid antigen elaborated by the parasite.

Cyst fluid as antigen. Most of the reliable serological work has been performed utilizing cyst fluid. Ghedini (12) used fluid derived from human sources, while Weinberg (13) prefers the clear fluid derived from cysts infesting sheep. Human hydatid fluid, according to this observer, is more frequently anti-complementary than sheep's, and in this animal the fluid from hepatic cysts is stated to be superior to that derived from pulmonary ones. Weinberg also studied the question of preservation of antigen in detail. He permits the addition of 5 per cent. phenol, but states that filtration is not so good. In my experience both methods are unsatisfactory and should not be used. An alternative adopted by him was to dry the fluid *in vacuo*. About 1·2 to 1·5 grm. of residue was obtained from every 100 c.c. of fluid. Prior to use the residue was dissolved in a corresponding amount of distilled water. Dr. Penfold, of the Commonwealth Serum Laboratories, has kindly undertaken the manufacture of this modified antigen. Thomsen and Magnussen (14) speak favourably of antigen paper infiltrated with cyst fluid and titrated.

Precipitates from cyst fluid. More recently Weinberg treated hydatid fluid with alcohol, centrifugalized and redissolved the precipitate in saline—this antigen he named the alcoholic residue. During the past year Patterson and the writer precipitated the globulin fraction with ammonium sulphate and also with magnesium sulphate. The precipitate so obtained was redissolved in saline and investigated for antigenic properties, but negative results were obtained.

Extracts of cyst fluid. Israel (15) and Meyer (16) believe that the antigen of the echinococcus is a lipoid, while Graetz (17) states that the protein of the hydatid cyst is derived from the host.

Parvu prefers an alcoholic extract of cyst fluid for antigen, while more recently Falcoiana (18) has used an ether extract, claiming for it superiority over all other antigens. Certain criticisms have been levelled against the alcoholic extracts, and though alcoholic extracts of cyst fluid are antigenic I have never found them as potent as the original fluid itself. Paisseau and Tixier (19) state that hydatid antigen is not completely soluble in alcohol and conclude in favour of plain hydatid fluid. Brauer (20) found that alcoholic extracts of cyst fluid showed pseudo-positive reactions with syphilitic sera, while Israel (21) demonstrated that similar extracts of daughter cysts did likewise.

The chemical nature of helminthic antigen. Much more work needs to be done on the biochemistry of helminthic protein or lipo-protein before any finality of opinion can be reached regarding this important subject. Whatever the chemical composition of helminthic protein, there is abundant evidence to show that alcoholic extracts of helminths do constitute true antigens. Thus Meyer (22) has demonstrated that the antigen of *Taenia saginata* is allied to lipoid or at least seems to be associated with lecithin. The writer (23) proved that alcoholic extracts of infested snails' livers (cercariae of *Bilharzia mansoni* and *Bilharzia haematobium*) constituted specific antigens for the reaction in bilharziosis. It will be seen later in this paper that alcoholic extracts of hydatid scolices constitute a specific antigen in the serological diagnosis of echinococcosis.

It is generally admitted that no protein-free antigens have been demonstrated. The fact that alcoholic extracts yield satisfactory results has led to the doubt whether these reactions are true Bordet-Gengou phenomena. Zinsser (24), however, has pointed out why such doubt is hardly justifiable.

Bang and Forssman (25) treated animals with ether extracts of red blood cells, claiming that this resulted in the production of haemolysins.

These results were confirmed by Dautwitz and Landsteiner (26), who suggested that the haemolysin production may have been induced, not by the lipoidal substance in solution, but by other antigenic substance which had gone into colloidal suspension in the ether extracts. Landsteiner (27) also comes to a somewhat similar conclusion, that, while no definite proof of the antigenic nature of any pure lipoid has so far been presented, the antigen may often be presented as a lipoid-protein combination and as such go into solution or fine emulsion in organic solvents; he also points out that lipoids have the peculiar property of altering the solubility of proteins and other substances by their own presence. Both the bilharzial and echinococcal alcoholic extracts used in these studies formed colloidal solutions.

The opinions of these authorities have been quoted in some detail, for it is important to realize that the antigens derived from the parasitic metazoa may have a different chemical constitution to the protozoal and microbic ones which have been mainly studied by immunologists in the past.

In order to investigate some of these problems a large number of observations and experiments was made on different hydatid fluids and on various saline and alcoholic extracts of hydatid elements.

A Comparison of the Relative Values of Human and Sheep Fluid as Hydatid Antigen.

The antigenic properties of over 100 specimens of hydatid fluid obtained from the lung and liver cysts of Australian sheep were examined. None of these fluids, many of which were pooled, were deficient in antigenic properties. The contention of Weinberg that the liver fluid of sheep is superior to that obtained from pulmonary cysts was not verified. In my series, fluid from both sources acted uniformly as efficient antigens.

On the other hand, out of eighteen specimens of hydatid fluid obtained at operation on man, four failed to act as antigens. In others antigenic properties, though present, were not as strongly developed as in specimens of sheep fluid. The antigenic value of hydatid fluid derived from humans, especially where the production of daughter and granddaughter cysts run apace, varies quite markedly. Occasionally fluids derived from different cysts within the same host and with a similar anatomical location possess different antigenic values.

During routine serological tests 180 cases (fifty-five of which were hydatid) were investigated by employing both human and sheep hydatid antigens. In all, fifteen different specimens of each were compared.

The 125 cases which were not hydatid were all negative. The results in the hydatid series are incorporated in the accompanying protocol.

PROTOCOL No. I.

A Comparison of the Serological Results obtained by Human and Sheep Hydatid Fluid.

Antigen.	Total Cases examined.	Total Cases positive.	Type of Reaction. Positive + + +	Positive + +	Positive +
Human	55	49	28	5	16
Sheep	55	50	36	3	11

In this series two cases of hydatid which were negative to sheep's fluid yielded positive results (P. +) with antigen derived from human sources, while three cases negative to human fluid were positive with that from sheep.

The actual superiority of hydatid fluid derived from sheep, when compared with human fluid, is shown rather in the intensity of the reaction than in the increase in the number of cases diagnosed. Note the greater frequency of strongly positive reactions (P. + + +) with sheep's fluid.

Concerning the Preparation of the various Antigens and their Relative Value.

Saline and alcoholic extracts of cyst contents were prepared as follows:

The *endocyst* or *ruptured daughter cysts* were washed free of hydatid fluid and cut into fine pieces. In the *saline extracts* (85 per cent. saline and 5 per cent. phenol) the hydatid membrane was ground up with sand in a mortar. The strength of the extracts varied between 10 and 25 per cent. After incubation for 24 hours or longer at 37° C. and repeated shaking, the extracts were filtered through paper. The filtrate was standardized before use, the necessary dilutions being made with normal saline (85 per cent.).

Alcoholic extracts were similarly prepared. Absolute alcohol was added to the membrane as it was being powdered in the mortar. The strength of different extracts varied between 10 and 25 per cent., while the period of extraction varied from one to seven days. Extracts were then filtered through paper, the filtrate in some experiments being concentrated by evaporation, utilizing a Sprengel's exhaust pump—a method which I have utilized with success in the preparation of other helminthic antigens (28).

The preparation of *scolex antigen* presented greater difficulties. Large quantities of hydatid fluid (20 oz. or more) were collected from the lung and liver cysts of sheep and the scolices were allowed to settle. The supernatant hydatid fluid was carefully decanted and the scolex sediment was collected. This was centrifugalized and twice washed with saline in order to remove all trace of hydatid fluid. It was subsequently ground up with sand and extracted with saline (85 per cent. saline, 5 per cent. phenol) or absolute alcohol as desired.

The strength of the extract was approximately 10 per cent., and after suitable shaking and incubation for 24 hours at 37° C. it was filtered and standardized.

The *method of standardization* employed for all these extracts consisted of an estimation of that concentration of antigen in unit volume which just fixed three minimum haemolytic doses of complement. One-third of the strength of this concentration was provisionally employed, and its complement binding power was tested out against syphilitic, normal, and hydatid sera. Where indicated, further appropriate dilutions with saline were made before the antigen was employed in routine serological diagnosis.

A series of experiments was then devised and carried out with the object of showing their differences in complement fixation.

The results showed that hydatid fluids from sheep cysts, lung or liver, possessed a uniform high scolex content and were invariably good antigens while human fluids which were poorer in scolices proved less satisfactory in this respect. Furthermore, the fluids obtained from sterile cysts containing no scolices were devoid of antigenic properties. In fact, the whole of the results obtained during the comparative study of sheep and human hydatid infestations suggested that the antigenic factor was independent of daughter and granddaughter cyst production and was in some way related to the scolex. This view has been fully supported by the experimental observations. The saline and alcoholic extracts of proliferating endocyst as well as of living and degenerated daughter and granddaughter cysts were all alike lacking in antigenic properties. On the other hand, both the alcoholic and saline extracts of scolices proved potent antigens.

The only two sources of hydatid antigen are the clear fluid and scolices. Why should inert hydatid fluid prove antigenic while actively proliferating mother endocyst is deficient in this respect? Surely it is because hydatid antigen is exclusively elaborated during the metabolic activities of the scolex which excretes or secretes it into the fluid medium in which it lives. Another possibility is that its origin is from dead and disintegrated scolices. No other hypothesis is tenable in view of the facts elicited during this investigation. Such a conception brings the test into line with other complement fixation reactions described in helminthiasis.

In bilharziosis, for example, the writer manufactured an antigen from the cercariae contained in the livers of infested snails and demonstrated antibody production in the sera of monkeys within six weeks of artificial infestation. Biologically considered, these cercariae are embryonic schistosomes. In analogous fashion we see that hydatid antigen is located in and elaborated by the scolex, which in reality is the embryonic tape-worm—*Taenia echinococcus*.

It is not advisable to subject the fluid to filtration or to add antiseptic. Both precautions are unnecessary, as uncontaminated fluid preserves its antigenic properties for many weeks if stored in dark glass receptacles in the ice-chest.

Both saline and alcoholic extracts of scolices yield highly potent antigens.

These alcoholic extracts may enable a stable concentrated antigen to be manufactured for general use.

Hydatid fluid in the amounts employed in these tests and experiments never acted as a syphilitic antigen. On the other hand, saline and alcoholic extracts of the cyst contents (i. e. endocyst, daughter cysts, and scolices) may act as *weak* syphilitic antigens if used in too concentrated solution. Careful standardization and appropriate dilution enables the serologist to work outside the danger zone of pseudo-positive reactions yielded by syphilitic sera.

A comparative study of sheep and human cysts and of the antigenic properties of the corresponding fluids demonstrated the existence of a definite relationship between the antigenic value of the fluids and their scolex content. A series of experiments subsequently verified these observations, and all the available data indicate that hydatid antigen is exclusively elaborated by the scolex, which excretes or secretes it into the fluid of the cyst itself. Another possibility is that hydatid antigen is derived from disintegrated dead scolices.

A Consideration of certain Factors modifying the Complement Fixation Reaction in Hydatid Disease.

Hydatid disease affords a unique opportunity for studying these alterations in the antibody content of the blood of infested patients occurring under natural conditions. The three essential factors involved in antibody production are: (i) Some protein or lipo-protein complex to act as antigen. (ii) Absorption of antigen by the circulating fluids in sufficient quantity and over a long enough period of time to stimulate the defensive mechanism of the host. (iii) A defensive mechanism capable of responding to the stimulus by elaborating specific antibody.

Absence of antibody from the peripheral blood of patients infested with echinococcal cysts may be due to failure of one, two, or all of these factors. These will now be considered in detail.

(1) *Hydatid Antigen.*

In the preceding section it has been shown that cysts devoid of scolices are lacking in antigenic properties. This is the case whether the cysts are sterile or whether they contain daughter and granddaughter cysts also. In other cases scolices, though present, are few in number, and here the fluids are only weakly antigenic. In hydatid cysts derived from human sources all types of fluid are met with—some are potent antigens, others possess but weak antigenic values, while occasionally the antigenic properties are absent.

Under these circumstances it is not surprising that negative reactions in patients' sera may be attributable to causes originating in the parasite itself. The following case illustrates this:

Case No. 124. Female, aged 34 years, was admitted to St. Vincent's Hospital complaining of an abdominal swelling which had been present for six years.

Examination revealed a movable tumour which was dull on percussion, and was located in the left lower quadrant of the abdomen. The complement fixation reaction was negative. At operation a pelvic hydatid of the left broad ligament was excised by Mr. Forbes Mackenzie. The cyst contained living daughter and granddaughter cysts; scolices, if present, must have been few in number as their presence was not noted. The antigenic value of this fluid was investigated and found to be practically nil. Some thirteen months later, on re-examination of the patient, the serological reaction and the Casoni intradermal test were both negative. The failure of antibody production in this case is to be attributed to the lack of antigenic properties in the cyst.

Occasionally, even where titration experiments have shown a low antigenic value in the hydatid fluid, a transient post-operative rise in the antibody content of the blood may occur, and a negative reaction, prior to operation, may become positive subsequently. While such a finding demonstrates that the fluid can act as an antigen provided a sufficient quantity is absorbed, it in no way invalidates the contention that the low-grade antigenic property of the fluid was responsible for the pre-operative negative result.

(2) *Factors modifying the Absorption of Antigen.*

The hydatid cyst is surrounded by a fibrous tissue barrier, the product of inflammatory reaction of the tissues of the host against the parasitic invader. This adventitia undoubtedly limits the quantity and the nature of the substances interchanged by the host and the parasite, and, as the writer[1] has shown elsewhere, may provide an effective protection for the cyst against intravenous medication with such a drug as tartar emetic. Food supply, gaseous interchange, and the removal of katabolites must operate via the tissue spaces and vessels of the adventitia, and where the capillary bed is obliterated by degenerative changes, calcification, &c., the parasite is frequently found dead. Where the parasite survives but is surrounded by a thick avascular adventitia, hydatid antigen can be absorbed only with great difficulty.

On the other hand, there are a number of factors which temporarily, at least, lead to increased absorption of hydatid antigen and may produce phenomenal rises in the antibody content of the circulating blood. Weinberg has dealt with certain of these in his later works (see references). Such causes as injury to the adventitia, partial or complete rupture of the cyst into the tissues or into a body cavity, surgical incision, and drainage, or recent suppuration all operate in this fashion. The effect of recent suppuration and recent rupture is illustrated in the following protocol:

[1] 'A Note on Failure of Tartar Emetic in the Treatment of Hydatid Disease,' shortly to appear in the *Medical Journal of Australia.*

PROTOCOL No. II.

The Relationship between the Serological Reaction and the Condition of the Cyst.

Condition of Cyst.	Number examined.	Number positive.	% positive.
Uncomplicated	45	34	75·6
Recent rupture (incomplete)	12	11	91·7
Recent suppuration	17	17	100

Note the greater percentage of positive reactions where these complications have supervened than in uncomplicated cases.

On the other hand, chronic suppuration producing death of the parasite and chronic abscess formation, complete rupture with evacuation of the cyst contents, and degeneration of the parasite all lead to the disappearance of antibody from the blood of the host. These facts are shown in the accompanying protocol.

PROTOCOL No. III.

The Relationship between the Serological Reaction and the Death of the Parasite.

Condition of Cyst.	Number examined.	Number positive.	% positive.
Chronic suppuration	2	0	0
Old rupture (complete)	3	0	0
Degeneration of parasite	11 *	0	0

* Six of these cysts were found at operation and five were demonstrated at autopsy in patients who died of intercurrent diseases.

(A) *The uncomplicated cyst.* In a number of patients with uncomplicated cyst I have been able to definitely prove that negative reactions were dependent on deficient absorption of antigen. In these cases it was found that: (1) prior to operation the serological test was negative; (2) the hydatid fluid obtained at operation possessed a high antigenic value when tested against other sera derived from hydatid cases; (3) after incision and drainage of the cyst, positive complement fixation reactions developed in the patients who previously were negative.

Since the fluid was antigenic and the patients' tissues elaborated antibody when antigen was absorbed following surgical intervention, it is certain that deficient absorption of antigen was the pre-operative factor responsible for the absence of antibody in this group.

Observations on five such cases are recorded below.

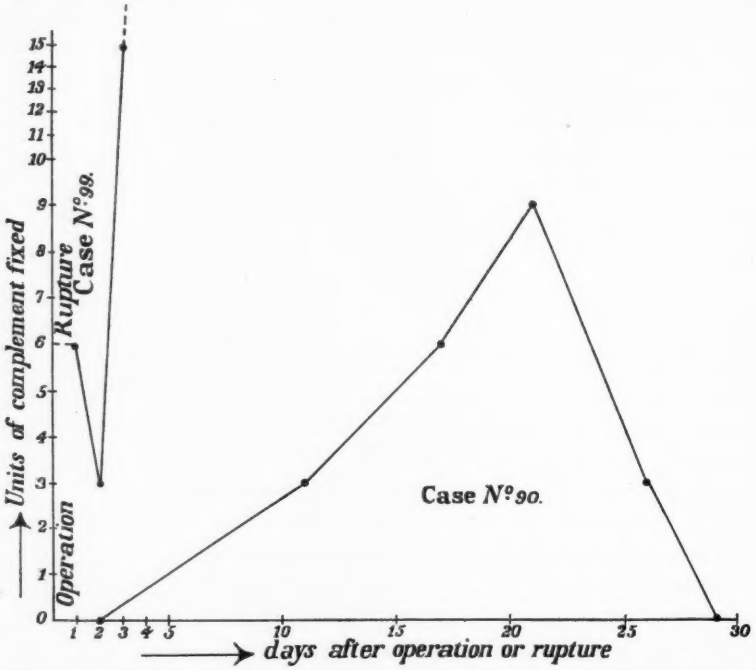
PROTOCOL No. IV.

Number.	Age.	Situation of Cyst.	Antigenic Value of Fluid.	Complement Fixation Reaction. Before Operation.	After Operation. 1st wk.	2nd wk.	3rd wk.	4th wk.	2nd month.
No. 5	32	Thyroid	Good	0	−	−	+	+	−
No. 86	15	Lung	Good	0	0	+++	+++	++	−
No. 57	$10\frac{11}{12}$	Liver	Good	0	0	−	+++	+++	+++
No. 90	$9\frac{10}{12}$	Liver	Good	0	0	+	+++	+++	0
No. 126	$8\frac{4}{12}$	Liver	Good	0	−	−	−	−	+++

0 = Negative. − = No examination. + = Positive.

In children it is not at all uncommon to find that negative reactions in the uncomplicated cyst are dependent on deficient absorption of antigen. This anomaly is dealt with in more detail in another section.

(B) *Operative interference.* The effect of operative procedure on the antibody content of the blood will naturally depend on the antigenic properties of the fluid and the absorption resulting from surgical intervention. Where, as in peritoneal hydatid, both the cyst and adventitia are excised whole, the complement fixation reaction remains quite unmodified. No fluid is absorbed. On the other hand, the more frequent procedure is to incise the adventitia which is left *in situ*, remove the cyst contents, and drain. Under these circumstances, hydatid antigen is freely absorbed and a post-operative rise in the antibody content of the blood is an almost constant phenomenon.



The cases cited in Protocol No. IV serve to illustrate the effect of operation where negative pre-operative serological results had been obtained. Similarly, quantitative methods show that cases yielding positive reactions before operation develop much more antibody as a result of surgical intervention.

In order to estimate the complement binding power of the patient's serum in the presence of hydatid antigen it is necessary to carry out titrations to an end-point and to employ quantitative methods. One should vary the dilution of the patient's serum, keeping the amount of complement constant, or vary the quantities of complement, keeping the amount of serum constant.

The accompanying graph illustrates the type of post-operative rise occurring in one case of this series (No. 90) where the latter method has been employed.

Following operation there is generally a measurable increase in the quantity of antibody by the end of the first week. The maximum of the rise occurs during the third and fourth week; thereafter a rapid fall ensues. Antibody, however, does not usually disappear from the peripheral blood as rapidly as is indicated in this graph. It is not infrequent to find a low-grade type of reaction (P+) persisting for several months after operation. This interesting and important phase of complement fixation work will receive more detailed consideration in a subsequent section.

(C) *Rupture of the hydatid cyst.* Rupture of the cyst almost invariably brings an increase of circulating antibody. In the series under consideration eleven out of twelve ruptured cysts yielded positive complement fixation reactions. Eight yielded positive + + +, two positive + +, and one positive + types of reaction. The increase in antibody may be very transient. This occurs when a cyst completely ruptures into a bronchus and the whole hydatid is coughed up. The reaction under these circumstances rapidly disappears. The absorptive power of the bronchial tree is not nearly as great as that possessed by the pleura or peritoneum, and serological examination may be negative even when an empty cavity can be demonstrated by X-rays. Where rupture of a pulmonary cyst is incomplete the reaction is more persistent, as hydatid antigen is absorbed over a longer period of time.

Rupture into a body cavity like the peritoneum or pleura is followed by a rapid increase in antibody. In one case—No. 90—a large hydatid cyst had ruptured into the peritoneal cavity. Following this event, on the second and third day there was a definite decrease in the antibody content of the blood (see graph above, Case No. 90) corresponding to the negative phase produced by over-inoculation. This fall was followed by a phenomenal rise, so that on the fifth day more than 15 units of complement were fixed, on the thirteenth day one-quarter the volume of serum normally employed fixed more than 36 units, and on the twenty-first day one-quarter the volume fixed 20 units of complement.

Evidently, here the maximum height of the curve was reached in the second and third week, the fall being definitely established by the twenty-first day.

The curve of the antibody content of the blood in all these conditions, the rapidity of its rise, the time incidence of the maximum, and the subsequent fall, will be determined by the antigenic properties of the fluid as well as the quantity and rate of absorption of hydatid antigen.

(D) *Suppuration of the cyst.* This complication, provided it is of recent duration, has always been associated with positive complement fixation reactions. In this series of seventeen cases of recent suppurative echinococcosis, seventeen, or 100 per cent., were positive. Twelve cases yielded positive + + +, two cases positive + +, and three cases positive + types of serological reaction.

Quantitative tests also show that cases of recent suppurating hydatid contain large quantities of circulating antibody. Where suppuration occurs in a dead cyst, or where this process has progressed for many weeks or months with early death of the parasite, naturally negative results are obtained. Such a finding was

recorded in two cases of our series, the final diagnosis being established only at autopsy.

Cultural investigations in suppurative hydatid suggest that there are two causes for this complication. Bacteria (such as *Bacillus coli, Staphylococcus aureus,* &c.) may localize in the adventitia, producing suppuration and death of the parasite (the pericystitis of Dupré). Here positive cultures are obtained. In other cases where cultures are sterile it seems possible that death of the parasite such as follows entry of bile into an hepatic cyst, or both these factors combined, may induce a secondary chemical inflammatory response culminating in suppuration. In either case the fibrous adventitia localizes the process and prevents overrapid absorption of toxic products. The clinical course of such a case is frequently afebrile. Despite this fact, however, suppuration of a living hydatid—provided the fluid is antigenic—is always accompanied by increased absorption of hydatid antigen. The death of the parasite and the increased blood-supply in the adventitia ensure that result. The first reaction to a degenerating or dying parasite is absorption of cyst fluid.

Under ordinary conditions the tension and amount of hydatid fluid within the cyst would appear to depend on two factors, namely, the rapidity of its production by the endocyst and the rate of its absorption via the adventitia. Death of the parasite would upset this balance in the direction of increased absorption. In addition, the accelerated blood-supply to the adventitia, consequent on inflammatory reaction secondary to bacterial toxins or chemical irritants, probably hastens on this process.

(E) *Death and degeneration of the cyst.* As indicated above, during the process of parasitic death hydatid fluid is absorbed, and at this stage a dying degenerating hydatid may yield a transient serological reaction. This phenomenon was observed in one case of the series. At first the reaction was strongly positive (P. + + +); within a fortnight the reaction had depreciated so that only a positive + reaction was recorded. Operation next day revealed a dying hydatid with bile-stained collapsed daughter cysts.

Absorption of hydatid fluid is followed by contraction of the adventitia on the cyst contents whether this consists of collapsed gelatinized cyst membrane or digested hydatid products. Ultimate calcification may ensue. Throughout all these subsequent stages of death and degeneration of the parasite the serological reaction is invariably negative. In eleven cases of old degenerated hydatids which were examined in this series all yielded uniformly negative results. In six of these cases the degenerative cysts were found at operation, but in the other five they occurred in patients coming to autopsy from intercurrent disease.

(3) *Failure of the Defensive Mechanism of the Host to elaborate Antibody.*

A consideration of this third possible explanation for deficiency of antibody in the peripheral blood of the host is rarely necessary. In only one case of our series was this factor held responsible for failure of the immunity response. The details are as follows:

Case No. 96. Male, aged 57 years, was admitted to hospital with the signs and symptoms of pulmonary and hepatic lesions; the temperature chart was remittent and intermittent in type. The patient died after being operated on for a subphrenic hydatid. There was no eosinophilia or leucocytosis. The total leucocyte count = 7,000 per c.mm. The Wassermann reaction was positive and tubercle bacilli were found in the sputum. Prior to operation the serological reaction was negative when sheep fluid was used as antigen, and positive with hydatid antigen derived from human sources. Re-examination of the blood one week after operation was negative. Investigation of the hydatid fluid, obtained at operation, showed that it contained scolices, while titration experiments proved its potent antigenic qualities. Autopsy revealed multiple echinococcal cysts.

A ruptured suppurative hydatid was noted in the right upper lobe of the lung. In addition, there were multiple hepatic, omental, and pelvic hydatids, and a splenic cyst. The right upper lobe of the lung also presented a tuberculous broncho-pneumonia. The base of the right lung showed pneumonic consolidation. There was a widely disseminated miliary tuberculosis of the left lung, and the mediastinal glands were also involved.

In this particular case the fluid was antigenic, and the absorbing surfaces of the various adventitiae were great. The small quantity of antibody prior to operation (P. +), and its absence after operative incision and drainage of the cyst, can only be explained on the basis of failure of the immunizing mechanism. When one contemplates the depressing action of the different toxins exerted on the tissue-cells producing antibody by such co-existing diseases as localized and disseminated tuberculosis, syphilis, acute lobar pneumonia, and secondary coccal infection of the pulmonary cyst, little difficulty will be experienced in accepting such an explanation for this case. As already indicated, however, such cases are rarely met with.

The Value of this Complement Fixation Reaction in Clinical Medicine.

In the preceding section data have been presented indicating the modification and the limitations imposed on the reaction by the state and condition of the parasite. An analysis of a large series of routine serological tests will now be recorded. The practical value of the reaction in diagnosis and prognosis can be ascertained from the incorporated protocols.

During the past eighteen months 1,070 cases have been investigated by means of this serological reaction.

Of these, 153 cases were suffering from, or had at some previous date been infested with, hydatid disease.

Cases not infested with hydatid. In 917 cases in which there was no evidence of echinococcosis the serological reaction was negative. In not a single instance was a misleading serological diagnosis made. In a number of cases of intra-abdominal tumours—including ovarian, omental, and pseudo-pancreatic cysts—the validity of the negative result was upheld at operation where previously a definite diagnosis of hydatid had been made on clinical grounds.

(A) *Syphilitic sera (135 cases).* In a preceding section we saw that certain saline and alcoholic extracts of cyst wall and of scolices were capable of acting as weak syphilitic antigens. Chemical analysis of hydatid fluid has shown a variable cholesterol content, and in consequence it becomes a matter of first importance to carefully test out the antigenic properties of sheep's hydatid fluid against syphilitic sera in case pseudo-positive reactions would result from syphilitic infections.

From this view-point 135 cases of syphilis yielding strongly positive Wassermann reactions were investigated. The following results were obtained:

PROTOCOL No. V.

The Hydatid Complement Fixation Reaction in Relationship to Syphilis.

Clinical Type.	Number examined.	Positive Wassermann.	Positive Hydatid Reaction.
Primary	10	10	0
Secondary	7	7	0
Tertiary	87	87	0
Latent	17	17	0
Congenital	11	11	0
Unclassified	3	3	0
Totals	135	135	0

No instance of the blood of a syphilitic giving a pseudo-positive reaction with the hydatid complement fixation test was recorded. The technique which was used has already been described in detail.

(B) *Helminthic infestations (8 cases).* Opportunities for studying other helminthic diseases have not been frequent, but wherever possible such observations were made. Every case was definitely negative, and my results entirely support those of Thomsen and Magnusson (14) on the specificity of the reaction. My series included four cases of bilharziosis (*Bilharzia haematobium*); two of *Ascaris lumbricoides*; a thread-worm infestation, *Oxyuris vermicularis*; and one with *Taenia saginata*. No tendency to pseudo-positive reaction was ever noted.

(C) *Other diseases (774 cases).* The sera examined were derived from almost every disease met with in hospital practice, and included pulmonary and hepatic lesions of every description, haematoma, abscess, tumours, malignant disease, abdominal cysts, acute abdominal conditions, and even systemic infections. Out of 774 cases examined negative serological results were consistently obtained and pseudo-positive reactions were never met with.

Perhaps the most remarkable feature of this important reaction is its *absolute specificity.* Non-hydatid sera haemolyse with such rapidity and certainty that no doubt remains in the mind of the serologist regarding the negative nature of the reaction. Uniformly negative findings in so large a series as 917 non-hydatid cases constitute the strongest possible evidence regarding the reliability of positive reactions when these are recorded.

The Diagnostic Value of the Reaction in Hydatid Disease.

A total of 153 cases of echinococcosis were examined. Frequently, repeated tests were made on the same person. The patients were either suffering from active cysts, from dead hydatids, or at some previous time had been more or less successfully operated on for this condition. In the latter group the blood was sent for re-investigation.

The case histories will be analysed according as the serological examinations were made at the time of or prior to operation, or at some date subsequent to operative interference.

(A) *Serological examination of cases infested with living hydatid at the time of or previous to surgical intervention.* In a preceding section the results obtained in a series of dead degenerated cysts and the modifying influence of certain complications, such as suppuration and rupture, were considered in detail, and will receive no further comment in this section.

Certain other factors, however, such as the age of the patient, the incidence of previous operation, and the site of the cyst, will be correlated with the serological results.

Regarding the diagnostic reliability of the reaction prior to operation a detailed protocol will be given, and case histories illustrating certain phases of the subject will be included. The general results obtained regarding pre-operative diagnosis in eighty-three cases of hydatid disease are incorporated in the following protocol:

PROTOCOL No. VI.

The Value of the Complement Fixation Reaction in Pre-operative Diagnosis.

Total Cases examined.	Number positive.	Type of Reaction.			Positive per centum.
		P.+++	P.++	P.+	
83	70	50	8	12	84·3 %

A few cases included in this series were examined for the first time at or within three days of operation. In the remainder the blood was collected prior to surgical interference. It will be remembered that for the first three days following operation the antibody content of the blood shows no increase: sometimes it is actually decreased. For this reason cases examined within this period can quite legitimately be included when assessing the value of the reaction in pre-operative diagnosis.

The high incidence of positive serological diagnosis (84·3 per cent.) in the above series conclusively proves the great value of the reaction in medicine. In thirty-one cases the clinical diagnosis had been definitely hydatid, but in the remainder it was either doubtful or echinococcosis had not been suspected. On the other hand, seventy out of the eighty-three cases were rightly diagnosed by the complement fixation reaction. I am convinced that the routine adoption of this test in medical practice would double the efficiency of clinical diagnosis in this disease and considerably lower the operative mortality.

The Effect of the Age of the Host and the Situation of the Cyst on the Complement Fixation Reaction.

In investigating cases of echinococcosis at the Children's Hospital, Melbourne, negative serological results were quite frequently obtained in definite cases of hydatid.

The relationship, therefore, between the age of the host and the complement fixation reaction was noted in seventy-seven cases of the series and is shown in the following protocol:

PROTOCOL No. VII.

The Age Factor and the Complement Fixation Reaction.

Decade.	Number examined.	Number positive.	Positive per centum.
1–10 *	11	7	63·6 %
11–20	7	4	57·1 %
21–30	16	15	93·7 %
31–40	14	12	85·7 %
41–50	13	11	84·6 %
51–60	12	11	91·6 %
61–90	4	4	100 %
Totals	77	64	83·1 %

* The youngest child of the series was aged 2½ years and suffered from a suppurative hydatid of the liver.

It will be seen that the most unsatisfactory results were obtained during the first two decades of life. Such a result was difficult to explain as the fluid from hydatids in children almost always contains scolices and is antigenic. Furthermore, all the cases investigated have developed post-operative complement fixation reactions. Examination of the adventitia shows it generally to be less fibrosed than that of the adult. What, then, is the explanation of the anomaly? In Protocol No. IV it was shown that uncomplicated cysts were responsible for more negative reactions than those in which suppuration or rupture had occurred. It would appear that the younger the host the less the chances of such complications. This may afford the explanation of the lower percentage of positive reactions observed during the first two decades of life.

Observations relating to the anatomical situation of the parasite did not suggest that this factor materially affected the reaction.

It would appear that the situation of cysts in the internal organs and peritoneum does not modify the reaction. On the other hand, hydatid involving muscle and bone did not give rise to as intense or as frequent a positive reaction as cysts elsewhere. Out of four cases examined, two were negative and two only yielded a positive + reaction.

The explanation of this finding is probably dependent rather on the antigenic properties of the cyst contents than on the location of the parasite within the tissues of the host.

PROTOCOL No. VIII.

The Anatomical Location of the Parasite and the Complement Fixation Reaction.

Situation.	Number examined.	Number positive.	Positive per centum.
1. Multiple	8	8	100 %
2. Liver *	40	34	85 %
3. Lung *	19	17	89·5 %
4. Peritoneum and pelvis	10	8	80 %
5. Spleen	1	1	100 %
6. Muscle and bone	4	2	50 %
7. Thyroid	1	0	0 %
Totals	83	70	84·3 %

* In ten of the liver cases and four of the pulmonary the location of the cyst was determined on clinical grounds. In all other cases their situation was demonstrated at autopsy or operation.

It is of interest to know that of the 83 cases under review 35 gave a history of previous operation for hydatid, and of these 32, or 91·4 per cent., yielded the reaction. Of the other 48 cases operated on for the first time, 38, or 79·2 per cent., were positive.

The Significance of Persistent Serological Reactions after Operation on Hydatid Cysts.

We have already seen that the absorption of hydatid antigen at operation or during subsequent drainage of the cyst leads to a marked and early rise in the antibody content of the blood, followed, in a period of fourteen to twenty-one days, by a fall to a lower level. Subsequently, the reaction may persist or entirely disappear. The significance of the modification of the post-operative curves and the exact time at which antibody may be expected to disappear in the event of effective operative intervention need careful study. Echinococcosis, more often than not, is a multiple infestation, and in consequence the question whether other cysts remain after operative intervention is one of great practical importance to the surgeon and patient alike. For eighteen months I have been collecting data bearing on this question, and propose to classify the facts according to the duration of time elapsing between the operation and the type of serological result obtained.

(A) *The type of reactions observed within twelve months of operation.* The actual observations made during the first twelve months are incorporated in the protocol on p. 264.

Four of these cases giving persistent positive reactions have proved at subsequent operations to have hydatid. During the first three months 47 out of 49 reactions were positive, whereas during the subsequent nine months only 21 positives were recorded out of 32 investigations. Antibody had disappeared from the blood of eleven cases. Four cases of this series in which persistent positive reactions were recorded were re-operated on within the twelve months and found to be again suffering from echinococcosis.

PROTOCOL No. IX.

The Complement Fixation Reaction in Patients operated on not more than Twelve Months previously.

Time elapsing since Operation.	Number of Cases examined.	Number positive.	Number negative.
1–4 weeks	32	30	2
2–3 months	17	17	0
4–6 months	16	10	6
7–9 months	8	6	2
10–12 months	8	5	3

When the individual case comes to be investigated antibody does not disappear with the regularity that might, on *a priori* grounds, be expected. My observations indicate that there are at least four groups of cases which may be met with. In *Group I* antibody is found in great quantity over a long period, the post-operative curve persisting at a high level or dropping only to rise subsequently within a short time.

In one patient the serological reaction was negative prior to operation, but subsequently large quantities of antibody appeared, which have persisted ever since surgical intervention (nine months). Here, owing to the inaccessible situation of the cyst, soiling of the peritoneum with fluid and scolices was inevitable. There is every reason to believe that the continued high-grade reaction in this case is due to fresh re-infestation produced by intraperitoneal sowing with the scolices spilt at operation.

In *Group II* antibody persists in medium quantity (P. + + and P. + + + reactions) over long periods after operation, i. e. for twelve months or longer. In several cases of this group re-operation has demonstrated persistent hydatid infestation. After the second operation the reaction may become negative.

Two cases gave strong reactions for many months subsequent to operation, and ultimately were successfully re-operated on. Another case was unsuccessfully explored, but subsequent X-ray examination has shown that the serological diagnosis was correct.

I regard the presence of a P. + + + reaction as absolutely diagnostic of another cyst where such a reaction is persistently positive twelve months after operation. Subsequent investigation may reduce the time factor to six months or less, but proof of this has not yet been established. More work is required over a longer period of time before this important question can be regarded as settled.

From the surgical viewpoint a post-operative positive reaction (P. + + +) of more than twelve months' duration may be regarded as diagnostic of a living cyst, and, provided there are reasonable grounds for suspecting its anatomical location, laparotomy is indicated.

In *Group III* of cases a mild grade of positive reaction (P. +) persists over many months. Subsequent to operative intervention there is a transient rise in antibody which soon falls but does not completely disappear from the peripheral blood. In Case No. 16 the reaction became strongly positive + + +

after operation and later decreased to negative. Four subsequent examinations were made; two were negative, and two were partial positive reactions (P. +). Later still, a P. + type of reaction developed, a swelling appeared in the lumbar muscles and re-operation showed recurrent hydatid cyst.

In a number of other cases in children the reaction was negative prior to operation, but thereafter became positive, and P. + types of reaction have persisted since. The Casoni intradermal cutaneous reaction has also been positive.

The exact significance of such findings is not clear. Whether they indicate recurrence or cysts elsewhere remains to be ascertained.

In *Group IV* the serological reactions are converted from positive to negative within a few months of operation and subsequently remain negative. Under these conditions and in the absence of clinical evidence of cysts elsewhere the chance of persistent infestation is remote. Such findings enable the surgeon to give an optimistic prognosis regarding the chance of recurrent echinococcosis.

(B) *The significance of positive and negative reactions in patients who have been operated on more than twelve months previously.* While the exact significance of persistent positive reactions during the first twelve months of operation is not always obvious, yet the data I have collected below can leave little doubt as to their significance subsequent to that date.

In the following protocol the incidence of positive reactions at different periods of time subsequent to operative intervention are correlated with the clinical and operative findings in individual cases:

PROTOCOL No. X.

The Complement Fixation Reaction as an Index to Recurrent Echinococcosis at Periods greater than one Year after Operative Intervention.

Time elapsing after Operation.	Number of Cases investigated.	Number of Positive Reactions.	Clinical Cases of Hydatid.
1-2 years	17	9	4
2-3 years	10	6	5
3-4 years	6	1	1
4-5 years	3	2	1
5-6 years	4	3	3
7-12 years	12	8	7
12-18 years	2	2	2
18-24 years	4	1	1
24-48 years	4	1	1
Unclassified (several years)	7	7	7
Totals	69	40	32

It will be noted that out of sixty-nine cases which at some period or other had been operated on for hydatid, forty yielded positive serological reactions. In thirty-two of these it was actually possible to prove the presence of hydatid infestation. With the remaining eight cases one can confidently assume that latent echinococcosis is present and that the subsequent history—if followed through—will confirm the serological diagnosis.

Summary.

1. Using the writer's technique, the complement fixation reaction has proved an absolutely specific test. In a series of 917 cases in which there was no clinical evidence of echinococcosis the serological reaction was negative. Neither the sera of syphilitics nor of patients infested with other helminthic disease give pseudo-positive reactions.

2. The serological data afforded by the reaction are of the greatest value to the surgeon in the preoperative diagnosis of echinococcosis.

In a series of 83 cases 70 (i.e. 84·3 per cent.) yielded positive results.

3. A certain minority of hydatid infestations yield negative complement fixation reactions. The causes underlying the non-appearance of antibody are due either to a deficiency in the antigenic properties of the parasitic fluid or lack of absorption of hydatid antigen through the adventitia. Rarely, where severe intercurrent diseases coexist, its absence may be traceable to a complete failure of the immunizing mechanism resulting from the poisoning of the tissue-cells elaborating antibody.

4. Certain complications of echinococcosis, such as partial or complete rupture of the cyst and suppuration, lead to a transient increase in the antibody content of the blood. Operative intervention when the cyst is drained produces a similar result.

5. The mechanism by which this increase is brought about is accelerated absorption of hydatid fluid. Death of the parasite from any cause—suppuration, entry of bile, &c.—immediately would appear to produce an upset of the balance between secretion and absorption in the direction of increased absorption. In addition the inflammatory reaction in the adventitia, whether primary or secondary, accelerates this process.

6. The effect of the absorption of echinococcal fluid on the antibody content of the blood of patients infested with hydatid is best studied as a result of operative intervention with drainage of the cyst. Quantitative titrations show a measurable increase in the quantity of antibody by the end of the first week. The maximal quantity generally appears during the third and fourth weeks and thereafter diminishes rapidly. Small quantities of antibody, however, may persist for several months after operation.

7. The diagnostic value of the reaction is considerably modified by the state and condition of the cyst. Thus, uncomplicated cysts yielded 75·6 per cent. of positive serological reactions, while those which had recently ruptured or suppurated yielded 91·7 per cent. and 100 per cent. respectively. On the other hand, old-standing suppuration, rupture with complete evacuation of cyst contents, and degeneration of the cyst invariably lead to negative serological findings.

8. It is noteworthy that the serological results were not as satisfactory during the first two decades of life as in older people. As explanation of this anomaly it is suggested that the increasing age of the parasite affords greater opportunities for the onset of those complications which raise the antibody content of the blood.

9. The significance of post-operation complement fixation reactions has been investigated in detail. Four groups of cases were noted during the first twelve months. While persistent strongly positive reactions over this period are indicative of active echinococcosis, the significance of the presence of smaller quantities of antibody has yet to be determined.

10. Persistent positive reactions of a period of one year or longer are indicative of active echinococcosis.

In a series of such cases 69 were investigated—40 were serological positives, and of these 32 were regarded as hydatid on clinical grounds at the time of investigation.

11. A more universal application of this reaction in clinical medicine will be followed by increased efficiency in the diagnosis of echinococcosis and lowering of the operative mortality.

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OBSERVATIONS ON CREATINURIA AND GLYCOSURIA IN MYASTHENIA GRAVIS

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Myasthenia gravis being a disease of voluntary muscle, which in female patients usually shows a remission during pregnancy, it was thought that there might be some change in creatin metabolism, and on examining the urine of a male patient on full hospital diet about 0·3 grm. of creatin was found daily for six days.

Examination of the literature showed that several investigations on metabolism in myasthenia gravis have been carried out. As early as 1906 Kaufmann (1) recorded a case in which he found acidosis and lactic acid in the urine. These findings have not been confirmed in other cases. Various authors (1, 2, 3) have recorded a retention of nitrogen and loss of calcium, together with an abnormally low creatinin excretion, while the patients were kept on a 'creatin-creatinin-free diet', but the investigation of creatin metabolism seems to have been overlooked to a great extent, for only two references to it can be found, and even then the results are not in agreement. Thus Diller and Rosenbloom (4) record that no creatin was present in the urine of a boy aged 16 with three months' history of the disease, while Bookman and Epstein (5) found creatin, varying in amount from 0·046 grm. to 0·036 grm. per diem, in the urine of a female patient aged 49 years.

Under the circumstances it was thought advisable to reinvestigate the problem so as to ascertain definitely whether or not a disturbance of creatin metabolism is a general feature of myasthenia gravis.

Methods employed.

The 'creatin-creatinin free diet' adopted was based on that used by Spriggs (2), the amounts being suited to the appetite of each individual patient, and kept constant as far as possible throughout the experiment. This diet was started three days before estimations were begun. Total nitrogen estimations were carried out as a check on the accuracy of the total amounts of urine collected. The daily excretion of urine was taken from 8 a.m. on one morning

to 8 a.m. on the following morning, chloroform being used to prevent bacterial contamination. Acetone and diacetic acid were tested for daily, but were never found. Sugar was also tested for daily, and at times a faint greenish reduction of Fehling's solution was obtained, which will be referred to later.

Creatin and creatinin were estimated in the first three cases by Folin's original method (6), hydrolysis being carried out in a 'steamer' at 96° C. for five hours. In Case 4 Folin's micro-method was adopted (7).

In Cases 1 and 2, where the amount of creatin excreted on the 'creatin-creatinin free diet' was found to be small, an attempt was made, by giving creatin by the mouth, to emphasize any defect there might be in the creatin metabolism. This was done by giving Liebig's extract containing an estimated amount of creatin and creatinin, milk of an equivalent nitrogen content being omitted from the diet on these days. Creatinin so given should be excreted almost entirely, thus serving as an additional check on the accuracy of the results. The patients were kept in bed throughout the experiment.

Case 1.

Male, aged 54; weight 11 stone 5 lb. Symptoms had been present for seven years, during which frequent partial remissions were observed. For the last two years symptoms were more severe and he was unable to follow any employment. Patient showed marked ocular disturbances with permanent ptosis. At times swallowing was difficult. He could walk as a rule, but became rapidly exhausted on attempting any physical labour.

On the 'creatin-creatinin-free diet' this man gave an average daily excretion of 0·047 grm. creatin and 0·939 grm. creatinin over a period of seven days. During three days he was given Liebig's extract containing a total of 5·36 grm. creatin and 5·95 grm. creatinin. During ten days subsequent to the initial dose of Liebig's extract, he excreted 2·75 grm. creatin and 5·201 grm. creatinin in excess of his former output (calculated on his average daily excretion) for a similar period. Thus, about 50 per cent. only of the creatin disappeared, and it will be seen by reference to Table I that at the end of this period the daily creatin excretion was still higher than the previous daily average of 0·047 grm.

After an interval on full diet some observations were made to confirm the preliminary estimations, and much larger amounts of creatin were found.

In spite of the patient's conviction that he had derived much benefit from the Liebig's extract, the administration of large quantities over a long period was found to have no therapeutic effect on this or subsequent cases.

Lactic acid was repeatedly sought for in the urine of this patient both during rest and after exhaustion of both arms, but no abnormal amount was ever found.

For full details of the case records see Table I.

TABLE I. *Case 1.*

The diet begun on January 17, 1921, consisted of:

Bread, 8 oz.	Butter, 2 oz.	Sugar, 2 oz.	Milk, 1 pint.	Eggs, 2 oz.
Rice, 1 oz.	Potatoes, 4 oz.	Oatmeal, 1 oz.	Cabbage, 8 oz.	Apple, 4 oz.

On January 23, 1¼ pints of milk were added to the diet. Estimations were begun on January 21.

Date.	Urine in c.c. per diem.	Creatinin in grm. per diem.	Creatin in grm. per diem.	Nitrogen in grm. per diem.	Remarks.
21	600	1·038	0·066	9·37	
22	635	0·905	0·047	9·52	
23	640	0·874	0·029	9·80	Diet modified, see above
24	1070	0·995	0·059	11·56	
25	825	0·965	0·025	10·35	
26	700	0·914	0·066	10·49	
27	1320	0·884	0·040	11·46	
28	1385	0·997	0·166	11·46	Liebig's extract given containing —
29	1260	2·369	0·580	10·51	creatin 2·07 grm., creatinin 1·53 grm.
30	1780	2·424	0·885	12·06	Repeated
31	1450	2·822	0·789	11·94	creatin 1·218 grm., creatinin 2·89 grm.
1	1050	0·987	0·273	10·23	
2	1285	1·131	0·167	11·78	
3	1000	0·830	0·070	7·90	Some urine lost
4	925	1·064	0·139	11·06	
5	1135	0·908	0·068	10·39	
6	1280	1·062	0·070	11·29	
11	1370	1·041	0·247		After 4 days on full hospital diet
12	1675	1·164	0·277		
13	1850	1·147	0·342		

Case 2.

Female, aged 28. Symptoms had been present for eight years. At times she was able to walk a few steps. While under observation she showed marked ocular symptoms. On some days she had to support her jaw with one hand, and was unable to raise her arms above the shoulder.

While on the 'creatin-creatinin-free diet' the daily average excretion determined after ten days was 0·0512 grm. creatin and 0·690 grm. creatinin. On two days Liebig's extract, containing a total of 1·26 grm. creatin and 2·46 grm. creatinin, was given as before. Estimations were continued for seven days, and during that period the patient excreted 0·464 grm. creatin and 2·52 grm. creatinin in excess of her former output (calculated on her average daily excretion) for a similar period. Thus about 36 per cent. of the creatin given was excreted.

TABLE II. *Case 2.*

The diet begun on February 18, 1921, consisted of:

Bread, 6 oz. Butter, 2 oz. Sugar, 2 oz. Milk, 2 pints. Eggs, 2 oz. Rice, 1 oz.
Potatoes, 2 oz. Oatmeal, 1 oz. Cabbage, 4 oz. Apple, 4 oz. Tea and Honey.

The diet was modified on February 20 in the following items:

Bread, 4 oz. Sugar, 1½ oz. Potatoes, 1 oz. Cabbage, 2 oz. Apple, 3 oz.

Estimations were begun on February 16, 1921.

Date.	Urine in c.c. per diem.	Creatinin in grm. per diem.	Creatin in grm. per diem.	Nitrogen in grm. per diem.	Remarks.
16	1000*	0·802	0·113		Estimations on normal diet
17	1000*	0·996	0·116		
18	1000*	0·788	0·097		
21	1000*	0·578	0·018	3·50	Estimations on 'creatin-creatinin-free diet'
22	1100	0·926	0·069	6·53	
23	1080	0·745	0·098	6·08	
24	1125	0·765	0·077	6·14	
25	920	0·684	0·039	5·46	
26	925	0·386	0·015	3·70	
27	665	0·642	0·040	6·29	
28	1435	0·990	0·083	12·13	
1	1070	0·802	0·060	6·89	
2	1175	0·382	0·013	3·72	
3	1125	1·935	0·180	11·06	Liebig's extract given containing— creatin 0·63 grm., creatinin 1·23 grm.
4	710	1·480	0·316	7·90	Repeated
5	870	0·918	0·090	8·84	
6	1060	0·791	0·063	7·39	
7	1010	0·758	0·043	7·10	
8	1280	0·722	0·059	6·86	
9	1090	0·747	0·071	6·87	

* Made up to 1000 c.c. with distilled water.

Case 3.

Female, aged 29; weight 8 st. 11 lb. 7 oz. Symptoms had been present for about three years. At first, patient was able to get about well, but could not do physical work. She had one child aged 6 months, and during the later half of her pregnancy was quite well. After her confinement symptoms returned worse than before. She had fallen several times from weakness. While under observation marked ptosis was present, and frequently she had to stop and rest before finishing meals. While on the 'creatin-creatinin-free diet' the daily average excretion, determined after fourteen days, was 0·0473 grm. creatin and 0·612 grm. creatinin. On full hospital diet the daily average was much increased. (See Table III.)

TABLE III. *Case 3.*

The diet was begun on March 23, 1921, consisting of:

Bread, 6 oz.	Butter, 2 oz.	Sugar, 2 oz.	Milk, 2 pints.	Eggs, 2 oz.
Potatoes, 2 oz.	Rice, 1 oz.	Oatmeal, 1 oz.	Cabbage, 4 oz.	Apples, 4 oz.
Tea and Honey.				

Estimations were begun on March 27, 1921.

Date.	Urine in c.c. per diem.	Creatinin in grm. per diem.	Creatin in grm. per diem.	Nitrogen in grm. per diem.	Remarks.
27	410	0·332	0·046	3·87	Estimations on creatin-creatinin-free diet
28	1380	0·758	0·153	6·39	
29	755	0·536	0·049	4·13	
30	680	0·529	0·042	3·14	
31	500	0·348	0·015	3·68	
1	570	0·553	0·034	3·80	
2	710	0·586	0·011	4·71	
3	920	0·861	0·027	5·90	
4	915	0·519	0·033	2·87	
5	510	0·449	0·037	3·40	
6	325	0·432	0·042	2·76	
7	970	1·013	0·069	8·34	
8	1340	0·817	0·054	4·90	
9	800	0·829	0·051	5·91	
16	650	0·444	0·111	4·69	On full hospital diet since March 9, 1921
17	820	0·586	0·136	5·74	
18	1100	0·825	0·198	5·51	

Case 4.

Female, aged 35; weight 8 st. 8 lb. Symptoms appeared five months before coming under observation and followed an acute attack of vomiting and diarrhoea. Weakness was first noticed in the back, later spreading to the legs, arms, and neck, so that her head fell forwards on her chest. She was then confined to bed and unable to move. Sphincter control was lost for a time, but regained later. For two months there had been difficulty in swallowing. Patient had been taking small doses of thyroid extract before coming under observation. This was suspended for three weeks before estimations were begun. At this time a squint was the only ocular symptom. There was general weakness of the muscles of expression and mastication. The patient was unable to sit up in bed without support, all muscles of the body being extremely weak; she was able to move her feet and ankles but could not raise the legs.

In this case the daily average excretion, determined after seven days on the 'creatin-creatinin-free diet', amounted to 0·449 grm. creatin and 0·184 grm. creatinin. (See Table IV.)

In the last three cases it was found difficult to procure complete specimens of urine, so that the average results obtained are minimal. Consequently, feeding with Liebig's extract was not attempted in Case 3, while in Case 4 it was thought that the change was so gross as to require no further demonstration.

The marked creatinuria observed in these four cases under different con-

ditions of diet indicates that myasthenia gravis is characterized by the presence of creatin in the urine. In bad cases this creatinuria may be very pronounced even when the patient is living on a diet practically free from creatin.

TABLE IV. *Case 4.*

The creatin-creatinin-free diet, begun on January 31, 1922, consisted of:

Bread, 6 oz.	Butter, 2 oz.	Sugar, 2 oz.	Milk, 2 pints.	Eggs, 2 oz.
Rice, ½ oz.	Potatoes, 1 oz.	Oatmeal, 1 oz.	Cabbage, 2 oz.	Apple, 4 oz.

Estimations were begun on February 3, 1922.

Date.	Urine in c.c. per diem.	Creatinin in grm. per diem.	Creatin in grm. per diem.	Nitrogen in grm. per diem.
3	1450	0·174	0·477	5·14
4	1000	0·117	0·279	2·74
5	920	0·160	0·253	3·90
6	1520	0·197	0·496	5·43
7	1700	0·223	0·555	7·71
8	1200	0·225	0·572	8·74
9	1250	0·195	0·513	7·94

Muscle Creatin in Myasthenia gravis.

Cases 1 and 2 volunteered to have small pieces of muscle excised for estimation of creatin. This was done under local anaesthesia and a little gas and oxygen, about 6 grm. of muscle being taken from the tensor fascia femoris. The creatin was estimated in portions weighing 2·5 grm. by Mellanby's extraction method (8), which gives a value of about 0·3 per cent. creatin for normal human muscle. The amounts found were:

Case 1 = 0·211 per cent.
Case 2 = 0·256 per cent.

It would, therefore, seem that the creatin content of these muscles is below the normal average.

Observations on Carbohydrate Metabolism.

During the urinary analyses small traces of sugar were found from time to time, suggesting that sugar tolerance was somewhat below the normal. To ascertain the sugar tolerance, tests were carried out on the lines described by MacLean and de Wesselow (9), the estimation of blood-sugar being done by MacLean's method (10).

In a normal individual the blood-sugar concentration varies within certain limits and is considerably influenced by the taking of food of a carbohydrate nature. If, for instance, a dose of 50 grm. of glucose be taken, the blood-sugar generally rises from the normal 0·1 per cent. to about 0·16 per cent. or 0·17 per cent. within thirty to forty-five minutes. After this initial rise, and while absorption is still going on from the intestine, there is a sudden fall in blood-sugar, chiefly no doubt owing to the action of the liver in removing the sugar

from the blood and storing it as glycogen. This mechanism, which in the case of glucose and several other sugars comes into play only after a certain rise in the concentration of blood-sugar has taken place, is helped to a considerable extent by the action of the muscles, for MacLean (11) has shown that during the stage of lowering of blood-sugar concentration after a dose of glucose the arterial and capillary blood contains more sugar than the venous blood. In myasthenia gravis it appears that the difference in sugar content between capillary and venous blood does not exist, for in Case 4 the following figures were obtained:

Capillary blood-sugar	(1) 0·125 per cent. (2) 0·121 „	Venous blood-sugar	(1) 0·120 per cent. (2) 0·121 „

Further, it is noteworthy that the rise in blood-sugar concentration obtained after a dose of say 50 grm., glucose is not increased, even if, instead of 50 grm., 100 grm. or more be taken, unless the carbohydrate metabolism is abnormal. Chart I, taken from MacLean and de Wesselow's paper, shows this well. Here the changes in blood-sugar concentration after doses of 50 grm. and 100 grm. of glucose are similar and the curves obtained practically identical.

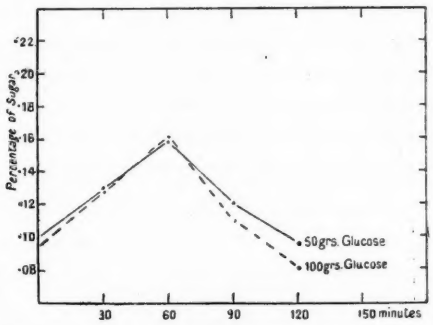

CHART I. Blood-sugar curve in normal subjects after ingesting 50 grm. and 100 grm. of glucose.

Even much larger doses than 100 grm. of glucose will not raise the blood-sugar any higher in normal subjects, though the top of the curve may be slightly more prolonged and the descent to normal slightly delayed. The point at which the kidney begins to throw out sugar in the urine is very near the maximum of blood-sugar concentration obtained after a fair amount of carbohydrate is ingested, but it is almost impossible, in a normal individual, to increase the blood-sugar to the concentration at which glucosuria occurs. Hence the normal subject does not have glycosuria however much sugar is taken, and the presence of glycosuria must mean some defect, permanent or temporary, in the carbohydrate metabolism.

Sugar tolerance tests were carried out on Cases 1, 3, and 4. In all of them it will be seen that 50 grm. of glucose produce little change from the normal curve, but that when 100 grm. were taken the difference was very marked. In Chart II, for instance, the ingestion of 100 grm. glucose resulted in a blood-

sugar concentration of about 0·23 per cent. after 1 hour, while after 2½ hours the concentration was still about 0·13 per cent. Fairly well-marked glycosuria was present, the urine containing 0·175 per cent. glucose after the first hour and 0·1 per cent. after two hours.

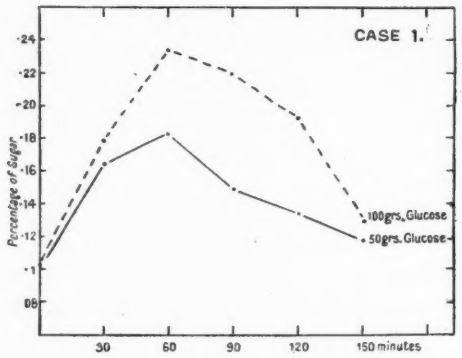

CHART II.

Case 3 gave a low but slightly prolonged curve after 50 grm. of glucose With 100 grm. the curve rose considerably and there was marked glycosuria.

Case 4 showed a slightly prolonged curve in view of the small rise after 50 grm. glucose, but after 100 grm. the curve rose much higher, and urine passed after 1½ hours contained sugar amounting to 0·38 per cent.

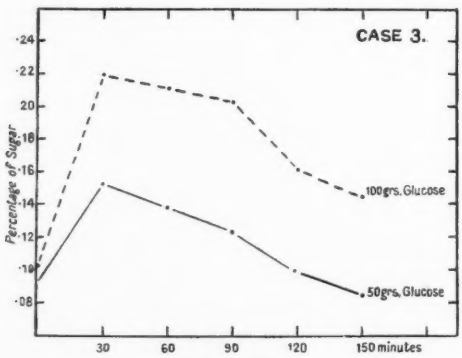

CHART III.

Since in all these patients there was an obvious lowering of carbohydrate tolerance, the natural inference to be drawn was that the defective muscles were responsible. Sugar in moderate doses was dealt with in the ordinary way, but slightly larger doses gave results altogether different from those obtained in normal subjects. Probably the liver is able to deal effectively with comparatively small amounts of sugar, but when larger amounts are ingested, muscle storage action may be necessary to maintain the normal curves. It

would seem as if this muscle effect was in abeyance in myasthenia gravis, and that the storage of sugar was chiefly carried out by the liver. That the liver seems to be quite as effective as it is normally, is supported by the fact that after 30 grm. of laevulose, no appreciable increase of blood-sugar took place (Chart IV). When the liver is defective, laevulose raises the blood-sugar, but this effect is not produced in the case of a healthy liver (MacLean and

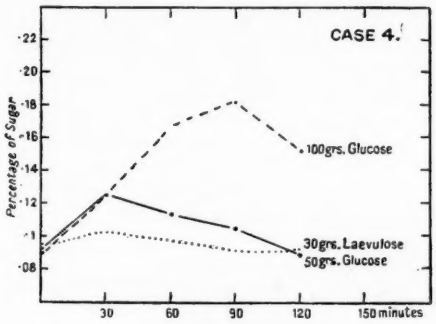

CHART IV.

de Wesselow (9), Spence and Brett (12)). Whatever the real explanation may be, there is no doubt that carbohydrate metabolism is quite abnormal in cases of myasthenia gravis, and it seems probable that the creatinuria observed is connected with this abnormality. This would conform with Benedict's (13) view of creatinuria resulting from defective carbohydrate metabolism.

Conclusions.

1. In the four cases of myasthenia gravis investigated creatinuria was present. In one case considerable amounts of creatin were passed while the patient was on a 'creatin-creatinin-free diet'. Inability to deal even with comparatively small amounts of creatin, when given by mouth, was observed in two cases. Creatinuria appears to be a definite feature of myasthenia gravis.

2. The two cases examined showed a somewhat low muscle creatin percentage.

3. This creatinuria appears to be connected with defective carbohydrate metabolism, the defect being probably located in the muscles.

Our thanks are due to Dr. Farquhar Buzzard for allowing us to use his cases, and to Sir Cuthbert Wallace for carrying out the surgical procedures referred to. We also wish to thank Professor MacLean for advice and assistance throughout the investigation.

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ON THE THERAPEUTIC VALUE OF QUINIDINE IN THE TREATMENT OF AURICULAR FIBRILLATION

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I. *Introduction.*

During August and September of last year (1921), Ellis and the writer tested the action of quinidine on seven cases of auricular fibrillation, and found that in five normal sino-auricular rhythm was restored.

Frey's original observations (1) and the results of other workers in the same field were therefore confirmed, and a preliminary report of our results was published in the *Lancet* (2). In this paper we emphasized the risk of the occurrence of embolism due to the expulsion of thrombi from the auricular appendices when auricular function is suddenly restored. We pointed out that in our cases the improvement in the patient's general condition was not pronounced, and concluded that while the physiological action of the drug in restoring normal rhythm was undoubted, the degree of risk in its administration and its value in therapeutics remained to be determined.

In the meantime, it has been thought desirable that one of us should follow up these cases, and continue to investigate the action of quinidine on cases of auricular fibrillation, with a view to collecting evidence from clinical observations to help towards the final solution of the following problems:

(i) The percentage of the unselected cases of auricular fibrillation in which quinidine may be expected to restore normal cardiac rhythm.

(ii) The best method of dosage of the drug.

(iii) Whether the simultaneous administration of digitalis in all or some cases assists, antagonizes, or exerts no effect on the action of quinidine in restoring normal heart rhythm.

(iv) The relationship, if any, of successful or unsuccessful quinidine therapy, and the dosage of the drug required to restore normal rhythm, to the condition of the heart as judged by:

(*a*) The pathological condition of the myocardium, i.e. rheumatic

[Q. J. M., July, 1922.]

myocarditis, cardio-vascular degeneration, bacterial endo- and myo-carditis, or the myocardial condition associated with exophthalmic goitre;

(*b*) The duration of cardiac symptoms;

(*c*) The severity of these symptoms;

(*d*) The valvular lesions;

(*e*) The duration of auricular fibrillation;

(*f*) The age and sex of the patient.

(v) The ill effects of administration of the drug:

(*a*) On the system generally;

(*b*) On the heart itself with special reference to disorders of rhythm, i.e. heart-block, the extra-systole, ventricular fibrillation, &c.

(*c*) The risk of embolism consequent on the sudden restoration of auricular function, and the relationship of this risk to previous embolic occurrences.

(vi) The value of restoration of auricular function in cases of organic myocardial disease as a therapeutic measure, and the possible relationship of this to the nature of the valvular lesion.

(vii) The relative value of:

(*a*) Restoration of auricular function with quinidine, and

(*b*) Control of ventricular rate with digitalis in the treatment of auricular fibrillation.

(viii) The contra-indications for the administration of quinidine.

(ix) The effect on the pulse-rate, blood-pressure, and urinary excretion of:

(*a*) Quinidine therapy *per se* when the auricles are still fibrillating;

(*b*) The restoration of auricular function;

(*c*) Quinidine *per se* after auricular function has been once restored.

(x) The prognosis and the tendency to relapse in those cases which have responded successfully:

(*a*) If quinidine is discontinued;

(*b*) If quinidine is continued indefinitely.

(xi) The effect of restoration of auricular function on the progress of coexisting disease with special reference to exophthalmic goitre.

(xii) Whether quinidine should be taken as a prophylactic against the occurrence of auricular fibrillation by patients suffering from certain forms of heart disease.

With these objects in view therefore, twenty cases of auricular fibrillation have been treated with quinidine and detailed clinical observations recorded. The results obtained from such a short series of cases are not sufficient evidence on which to base any general conclusions, but our knowledge of this subject is still in its infancy, and as a method of treatment it is beset with many possibilities and many dangers. Accordingly it has been considered advisable to publish the results obtained in the first twenty cases. This series includes the seven cases already published in the *Lancet*, and their subsequent clinical histories up to the time of writing. In a later communication it is hoped to publish a further series of cases, together with the subsequent clinical histories of the first twenty. Then

perhaps enough evidence will have accumulated on which it will be possible to base certain general conclusions as to the value of quinidine in the treatment of auricular fibrillation.

While our first paper was in the press Drury and Iliescu (3) reported thirteen cases of auricular fibrillation treated with quinidine, in six of which sino-auricular rhythm was restored. The electro-cardiographic records obtained showed auricular fibrillation passing into normal rhythm by way of impure flutter, but in one case only was true flutter produced. The auricular rate fell, and the ventricular rate rose with the administration of the drug, and they considered it advisable not to force the auricular rate above 200 lest a 1 : 1 ventricular response and a consequent high rate of beating were produced. They reported no case of embolism or any other serious results of the administration of quinidine.

At the same time Lewis, Drury, Iliescu, and Wedd (4) showed that quinidine has two actions on cardiac muscle; it lengthens the refractory period and slows the conduction time. They point out that these two actions are antagonistic in bringing the circulating wave which underlies auricular fibrillation to an end, and that it is only in those cases in which the first effect of the drug predominates over the second that a successful result can be expected.

On reading these papers, Mackenzie (5) uttered a warning on the danger of embolism when sino-auricular rhythm is suddenly restored, and Orr (6) quoted a case in which embolic infarction of the brain and radial artery occurred when normal rhythm was restored in a case of auricular flutter.

A little later Hewlett and Sweeney (7) reported restoration of normal rhythm in five out of eleven cases. Of these five successful cases, one was a case of the paroxysmal type in which normal rhythm was restored after a very small quantity of the drug had been given. In another normal rhythm only lasted a few days, was interrupted by ventricular extra-systoles, and relapse into fibrillation occurred almost immediately the drug was discontinued, the patient dying a few days later. In a third subsequent to the restoration of normal rhythm heart-block occurred after a very small dose of digitalis. With the exception of the case that died all these patients showed some improvement, and in one case signs and symptoms of failure which failed to yield to digitalis therapy cleared up completely when sino-auricular rhythm was restored with quinidine. With the exception of the death referred to, which the authors do not attribute directly to the action of the drug, the only untoward results observed were nausea, anorexia, vomiting, and an increase in ventricular rate and softness of the pulse. In a foot-note to their paper, however, these authors report the case of a patient in fairly good compensation who died shortly after normal rhythm had been restored with quinidine. They also review the reports of other workers in the same field, and give a useful analysis of the results obtained and the general conclusions arrived at.

In the same number of the same Journal Hamburger (8) reported restoration of auricular function in three out of seven cases of chronic auricular fibrillation. In two definite clinical improvement is recorded, but the general condition of the third remained unchanged. Two developed auricular and ventricular extra-

systoles after restoration of normal rhythm, and all three showed a definite bradycardia. In one case normal rhythm remained permanent, but in the other two relapse into fibrillation took place soon after the drug was discontinued. In one case of paroxysmal fibrillation the paroxysms were shortened, and subsequently occurred less frequently.

Again, in the same number Oppenheimer and Mann (9) report twenty-two cases of chronic auricular fibrillation treated with quinidine, in nine of which normal cardiac rhythm was restored, and in two of which either pure or impure flutter was produced. In the majority of these patients definite clinical improvement was recorded, and no severe untoward symptoms attended the administration of the drug.

The present position of our knowledge of the action of quinidine in cases of auricular fibrillation may be summarized as follows:

1. Between two and three hundred cases have now been treated with quinidine and the results reported in the literature. In about one-half of these cases normal sino-auricular rhythm has been restored, and in a small proportion of the unsuccessful cases transient auricular flutter has been produced.

2. Quinidine acts by prolonging the refractory period and decreasing the conductivity of heart-muscle. During the administration of the drug the auricular rate falls and the ventricular rate rises, due to lessening of fatigue in the auriculo-ventricular bundle. The transition from fibrillation to normal rhythm takes place usually through impure, and occasionally through pure flutter.

3. The number of successful cases runs approximately parallel with the dose of the drug employed. Thus Jenny (10), who gave as much as 46 gr. of the drug per diem, obtained 94 per cent. of successes.

4. The action of quinidine in restoring normal rhythm is most successful in those cases in which auricular fibrillation is of short duration. On the other hand, many successful results have been observed in cases in which the disease was known to have been present for two or three years.

5. The degree of decompensation influences the action of quinidine unfavourably. But Benjamin and v. Kapff (11) state that the degree of decompensation in which the patient is first seen is of less importance than the degree of compensation to which the patients can be brought by treatment. These authors therefore advise a preliminary course of digitalis in all cases exhibiting decompensation.

6. If the drug is discontinued tendency to relapse seems to be the rule, and there is some evidence in the literature that if the drug is continued relapse is less likely to occur.

7. That in the majority of successful cases there is some definite improvement in the objective and subjective clinical conditions of the patient. In many cases there is no change, and in a few cases the patients are definitely worse. In some cases symptoms and signs of failure, which did not disappear under digitalis, have yielded completely to quinidine therapy.

8. The commonest untoward symptoms of administration of the drug

observed are nausea, anorexia, vomiting, &c. The ventricular rate usually rises and symptoms and signs of increasing decompensation may occur.

9. Alarming symptoms—sudden pulselessness, cyanosis, apnoea, and unconsciousness—have been observed in a few cases. Frey (1) has reported two such cases. But in neither case did death occur. It is interesting to note in this connexion that Schott (12) states that in animals intoxication with quinidine leads to sudden cessation of respiration. Several fatalities are recorded in the literature, but it is difficult to say in these cases whether the cause of death is definitely attributable to the drug. In addition to the two fatal cases reported by Hewlett and Sweeney and already referred to, v. Bergmann (13) reports two cases in both of which the heart was badly decompensated. One of these died four days after quinidine had been stopped, and the other shortly after a relapse into fibrillation had occurred and when quinidine was again being administered.

Benjamin and v. Kapff (11) report two fatal cases, one of which died of broncho-pneumonia and the other a case fairly well compensated, but which reacted to quinidine with praecordial pain and respiratory distress, and died soon after normal rhythm was restored. These authors also call attention to the risk of embolism, reporting one case of pulmonary infarction, and attribute the above case and the alarming symptoms in one of Frey's cases to this cause.

10. At present there seems to be no relationship between successful restoration of normal rhythm and the etiological cause of the myocardial disease. All types of cases, rheumatic, degenerative, or associated with exophthalmic goitre, seem to react or fail to react in approximately equal proportions.

II. *Theoretical Considerations.*

The physiological function of the heart is the maintenance of a circulation of the blood which is adequate to supply the oxygen demands of the tissues. When the oxygen supply of the tissues is insufficient signs and symptoms of failure supervene. The mechanical efficiency of the heart as a whole in the performance of this function depends upon three chief factors:

1. The functional efficiency of the myocardium as a source of kinetic energy.

2. The functional efficiency of the valves in preventing regurgitation of blood, and the patency of the valves in offering the minimum of resistance to the flow of blood through them.

3. The maintenance of an orderly rhythmic contraction of its component chambers.

Whenever one or more of these factors are interfered with, the heart has now to do more work to maintain adequate circulation. The reserve force of the heart is therefore encroached upon, and unless corresponding hypertrophy occurs, the field of cardiac response to increased load is diminished, and the functional efficiency of the heart as a physiological organ is decreased.

The heart may therefore be subjected to three important handicaps in the performance of its function. These may be referred to conveniently as the myo-

cardial, the valvular, and the rhythmic. In all those hearts about to pass into the condition known as auricular fibrillation, the myocardial handicap and, in the majority of cases, a serious valvular handicap (mitral stenosis) are both already present. In such hearts hypertrophy is usually insufficient to compensate entirely for these handicaps, and there is consequently already some encroachment on their reserve force. The field of cardiac response to exercise is therefore almost invariably reduced, and the functional efficiency of these hearts is subnormal before the onset of fibrillation occurs.

When auricular fibrillation supervenes in such patients an additional handicap (rhythmic) is thrown upon these already inefficient hearts for the following reasons:

A. Incomplete diastolic filling of the ventricles, due to absence of auricular systoles and the interposition of a passive dilated bag between the great veins and the ventricles instead of a contracting auricle.

Though it is probably true that in the normal individual at rest ventricular filling is probably complete before auricular systole commences, during the tachycardia and the shortened diastole associated with exercise in the normal person, during the tachycardia associated with myocardial disease, and almost certainly under resting conditions when mitral stenosis is present, auricular systole is necessary to complete ventricular diastolic filling.

B. The fibrillating auricle stimulates the ventricle in a rapid and irregular fashion and irrespective in both force and time of the degree of ventricular filling which has been allowed to occur. A great deal of the mechanical energy of the ventricular systoles must therefore be wasted, and the ventricular musculature probably never gets a rest which is much longer than its natural period of recovery from the refractory period.

C. When the auricles are in fibrillation the sino-auricular node or pacemaker of the heart ceases to control the ventricular rate. It is the sino-auricular node which of all parts of the heart is most under control of the nervous system. In auricular fibrillation, therefore, the ventricular rate is no longer adjusted, as in the normal heart, by vagal reflexes to the rate of diastolic filling and the peripheral resistance.

Therefore it is not surprising that when this serious rhythmic handicap is superadded to an already inefficient heart, struggling with pre-existing myocardial and valvular handicaps, an attack of failure should occur. The reserve force of the heart is suddenly encroached upon to such an extent that it cannot maintain adequate circulation of the blood and satisfy the oxygen needs of the tissues even at rest.

In certain cases, and under certain circumstances, admittedly heart failure does not occur when auricular fibrillation suddenly supervenes. These cases may probably be classified under three heads:

1. When the myocardium is comparatively slightly affected by disease, and the heart as a whole has plenty of reserve force to meet the new handicap suddenly thrown upon it.

2. When the change occurs when the patient has been resting in bed.

The heart is lightly loaded, and even in the presence of myocardial degeneration the heart as a whole has sufficient reserve force to deal successfully with the new handicap which has been suddenly imposed.

3. In some cases of mitral stenosis in which symptoms of failure and marked tachycardia precede the onset of fibrillation. In these cases nature has probably overshot the mark: the tachycardia exceeds what is functionally efficient under the existing circumstances. When the onset of fibrillation occurs, the ventricle is freed from sino-auricular control, and the pulse-rate, especially if a partial degree of heart-block exists, now falls. The patient consequently experiences relief, as the mechanical efficiency of the heart as a whole has risen.

We have now two methods of treating auricular fibrillation:

1. *Digitalis.* By the exhibition of digitalis we can produce partial heart-block. By this procedure we cut off the weaker stimuli from the auricles, the ventricular rate is slowed, a longer period of rest follows each ventricular systole, and the most inefficient ventricular beats are eliminated. The auricles are, however, still fibrillating, auricular systoles are still absent, the ventricular action is still irregular, and only an artificial ventricular rate has been established. We do not know if this artificial rate is the most economical under existing circumstances, and the reflex method for the adjustment of pulse-rate to diastolic filling and peripheral resistance has not been restored.

Such a method of treatment is symptomatic and palliative, and does not get at the underlying cause of the ventricular irregularity.

2. *Quinidine.* By the administration of quinidine we can in the majority of cases restore auricular function. The heart is again dominated by its normal pace-maker, auricular systoles occur and are followed regularly by ventricular systoles, the ventricular action is regular, and the heart-rate can be adjusted through the agency of nervous reflexes to the rate of diastolic filling and the peripheral blood-pressure.

On theoretical grounds, therefore, the restoration of auricular function which can be brought about by the administration of quinidine, other things being equal, should be a more successful therapeutic procedure than the symptomatic treatment of auricular fibrillation by the artificial control of ventricular rate with digitalis.

But we must not expect the restoration of auricular function in these cases to work wonders.

All hearts in which auricular fibrillation is present are the victims of myocardial disease, and in the large majority a serious valvular handicap is present as well. Such hearts are already frequently inefficient to a serious degree when fibrillation first supervenes. No therapy can ever restore the functional efficiency of a diseased valve, or restore a degenerate myocardium. Of the three handicaps that are commonly imposed upon the heart, the rhythmic is the least severe, and therefore all we can expect of quinidine is to restore the heart to the same level of mechanical efficiency as existed in that patient immediately prior to the onset of fibrillation.

Setting aside all theoretical considerations, an attempt has now been made

to determine from clinical observation, whether the restoration of sino-auricular rhythm in cases of auricular fibrillation does or does not lead to a rise in the efficiency of the heart as a whole in the performance of its function, and, if so, whether the rise in cardiac efficiency so produced is equal to, greater or less than, the rise previously produced in the same heart by digitalis alone.

In this way only can we arrive at a comparison of the relative merits of quinidine and digitalis in the treatment of this condition.

III. *The Estimation of Rise or Fall in Cardiac Efficiency.*

To make the comparison referred to in the last section, it is obvious that we must have a method of estimating rise or fall in cardiac efficiency. Unfortunately, we have no instrumental or numerical method, and we have to rely entirely upon:

1. The patient's own statement of his or her subjective symptoms.
2. Clinical observations of certain physical signs.

Two methods are adopted, overlapping to a certain extent it is true, but corresponding roughly to two periods in the course of treatment to which each patient is subjected.

A. During the period of transition from decompensation to compensation, while the patient is resting in bed and being treated with digitalis, we make our estimate of increase in cardiac efficiency by observing, in addition to diminution in severity of the patient's subjective symptoms, the change in certain objective signs.

B. When compensation has been re-established physical signs fail us completely, and to estimate any rise in cardiac efficiency that may have occurred as the result of our treatment, we inquire into the amount of work the patient can do without leading to the appearance of cardiac symptoms. We take this amount of work as the index of cardiac efficiency.

An attempt has been made in the following series of cases to estimate the alteration in cardiac efficiency at three chief periods in the treatment of these patients:

1. Immediately after sino-auricular rhythm is restored.
2. When the patient is allowed up, and discharged from hospital.
3. After discharge from hospital when the patient returns to work or household duties.

On admission, the average patient of this series is in a condition of failing compensation or acute heart failure. He or she is put to bed and treated with digitalis. In the course of time compensation is partially or completely restored. There has now been a definite rise in cardiac efficiency as judged by the disappearance or diminution of symptoms and signs of failure. Digitalis administration is now discontinued and quinidine commenced. The patient usually goes downhill a little, due to the toxic action of the drug on the system generally. In a few with the cessation of digitalis signs and symptoms of failure may re-

appear. In the majority of cases normal sino-auricular rhythm is suddenly restored, and from observation on signs and symptoms we can now draw certain conclusions.

A. If digitalis has previously restored compensation completely, i.e. if signs and symptoms of failure have completely disappeared, and there has been no relapse in the direction of failure, the restoration of auricular function cannot affect the clinical condition of the patient, and we have no evidence whatever that this procedure has produced any rise in cardiac efficiency.

In some cases, however, these patients, even when completely compensated under the action of digitalis, complain of subjective sensations in the chest, fluttering, palpitation, or consciousness of the heart's action. Should restoration of normal rhythm abolish these symptoms, though no doubt it will add greatly to the comfort of the patient, it will by itself afford no evidence of increased efficiency of the heart.

B. If the patient after rest in bed and prolonged digitalis treatment still shows signs and symptoms of failure, i.e. if digitalis alone has failed to completely restore cardiac compensation, then if the restoration of auricular function leads to disappearance of these signs and symptoms, we have definite evidence that this procedure has raised cardiac efficiency to a higher level than digitalis alone could do.

In the large majority of cases digitalis and rest in bed restore cardiac efficiency to such a level, that while the patient is in bed signs and symptoms of failure remain absent; also when digitalis is discontinued for a few days relapse into failure seldom occurs. It follows, therefore, that the signs and symptoms of failure being absent immediately prior to the restoration of auricular function, it cannot possibly be expected that this procedure will produce any dramatic change in the patient's condition. At this juncture we cannot therefore expect to obtain much evidence of the relative values of digitalis and quinidine in the treatment of the condition.

The patient is now allowed up, and gradually begins to walk about and assist in the lighter work of the ward. At this stage we can again draw certain conclusions.

A. If the signs and symptoms of failure abolished by digitalis now remain completely absent, and if digitalis has been discontinued and normal sino-auricular rhythm restored, we can say that this procedure is at least maintaining the same level of cardiac efficiency as digitalis alone.

B. If the signs and symptoms of failure abolished in the first place by digitalis now reappear, although normal rhythm has been restored, then this procedure is maintaining either the same or more probably a lower level of cardiac efficiency than digitalis alone.

The patient is now discharged from hospital to return home, and probably to work or household duties. It is at this stage that we must expect to draw our most important conclusions, but for this purpose the cases must be divided into two groups:

Group I. Which includes all those cases in which auricular fibrillation has been of comparatively short duration, and which prior to their last admission to hospital, when they were first treated with quinidine, had received no digitalis therapy. In these cases, unless quinidine is going to restore compensation completely when digitalis partially failed, we cannot estimate the value of the two methods of treatment because we have no standard of comparison. Therefore, we can only estimate whether the quinidine treatment of fibrillation is equal or inferior to the digitalis treatment of the same condition in raising the level of cardiac efficiency.

Group II. Which includes all those cases in which auricular fibrillation has been known to be of long duration, and which have received digitalis treatment prior to their first admission to hospital for quinidine therapy. In these cases we have a definite standard of comparison, and we can compare the efficiency of the heart with fibrillating auricles and irregular ventricular action controlled by digitalis with the efficiency of the same heart when normal sino-auricular rhythm has been restored.

If in Group I it can be shown that the patient can do as much work, and take as much exercise without the appearance of symptoms and signs of failure, after the restoration of normal rhythm as at any time before the probable date of onset of fibrillation, then quinidine is at least equal to digitalis in raising the level of cardiac efficiency.

If in Group II it can be shown that after the restoration of auricular function with quinidine the patient can do more, less, or an equal amount of work without the appearance of cardiac symptoms than during the period when the auricles were fibrillating and the ventricular rate controlled with digitalis, then we have evidence that the restoration of normal sino-auricular rhythm is of either greater, equal, or less value respectively compared with digitalis in raising the level of cardiac efficiency in this condition.

Lastly, if it can be shown that in Group II quinidine is of greater value than digitalis in the treatment of auricular fibrillation, the same probably holds true for Group I, in which, owing to the absence of a standard of comparison, this contention cannot be proved directly.

IV. *Methods.*

I. *Cases.* All cases of auricular fibrillation which have been recently admitted to the Medical Unit wards have been submitted to quinidine treatment, irrespective of age, sex, the duration of cardiac symptoms, the nature of the pathological lesion, the severity of the myocardial condition, and the coexistence of other morbid conditions; provided only that compensation while the patient was resting in bed could be partially restored with digitalis.

It has been considered unjustifiable, and from the results of other workers it would appear useless, to treat cases of the disease in a condition of acute cardiac failure or with failing compensation with quinidine. Therefore these cases

which did not respond to digitalis, and in which severe signs of failure persisted, have not been subjected to quinidine treatment. Apart from this, no selection of cases whatever for the purposes of this research has been exercised.

The series includes, with the above exceptions, all cases of the disease which have passed through the Medical Unit wards during the last half-year, and also comprises, owing to the kindness of the physicians to the hospital, who have allowed cases primarily under their charge to be transferred to the Medical Unit for the purposes of this research, the large majority of patients suffering from auricular fibrillation who have been admitted to the hospital over the same period.

II. *Histories.* In each case a detailed clinical history of the patient's illness has been taken, with special reference paid to the following important points:

1. A history or a family history of acute rheumatism, rheumatism, chorea, or other manifestation of the rheumatic diathesis.

2. The duration of cardiac symptoms.

3. The probable duration of auricular fibrillation. In some cases, from previous admissions of the patient to hospital, auricular fibrillation is known to have been definitely present or definitely absent over certain periods, but the actual date of onset of fibrillation could in all cases only be inferred from the patient's history, and in some cases even this was impossible.

4. A history of symptoms or hospital records suggestive of previous embolic occurrences.

III. *General management.* All cases with failing compensation have first been treated with digitalis alone until signs and symptoms of failure have largely disappeared, and the patient was fairly well compensated at rest in bed.

Digitalis has then been discontinued and quinidine administration commenced either immediately or after a short interval. All cases of the disease under quinidine treatment prior to the restoration of auricular function have been kept strictly in bed, and it has not been considered justifiable, in view of the known risks of the treatment, to treat out-patients in this manner.

IV. *Dosage of the drug.* During the treatment of the first seven cases no particular method of dosage was employed. For the remainder, however, a standard but arbitrary system has been adopted. Quinidine, gr. v six-hourly, is given to start with and continued for 72 hours. The dosage is then increased gr. i per diem until either normal sino-auricular rhythm is restored, or until for other reasons further administration is contra-indicated.

The patient thus receives gr. vi six-hourly on the fourth day, gr. vii six-hourly on the fifth day, and so on.

In the present state of our knowledge, we do not know if relapse into fibrillation will occur when the drug is discontinued. It seems natural to suppose, however, that when quinidine is stopped the factors which led originally to the sudden development of fibrillation will reassert themselves, and therefore, on *a priori* grounds, if the drug is discontinued relapse is to be expected sooner or later.

Seeing that the sudden onset of fibrillation is usually associated with an attack of heart failure, and in view of the precarious myocardial condition of the majority of these patients, it has not been considered justifiable to run the risk of allowing relapse to occur. Therefore when normal sino-auricular rhythm has been once restored, the quinidine dosage is gradually reduced gr. i per diem until gr. v, bis die, is reached. The patient is then discharged with instructions to continue taking this amount of the drug. Should relapse occur in spite of this, the dosage has been again increased until sino-auricular rhythm is again restored. Then the drug is again reduced and an attempt is made to discover the minimum amount of quinidine which will maintain normal cardiac rhythm.

V. *Simultaneous administration of digitalis.* Except in one or two of the earlier cases digitalis has not been administered simultaneously with quinidine. When, however, what was considered to be the maximum safe dosage of quinidine had been arrived at without normal rhythm being restored, then in some cases digitalis has been combined with quinidine with the idea of attempting to discover if digitalis in any way assists quinidine in this action.

VI. *Pulse-rate records.* A two-hourly pulse chart has been kept by the nursing staff during the whole period of administration of the drug.

VII. *Blood-pressure observations.* Though accurate observations on blood-pressure undoubtedly cannot be made, the writer believes that a mean blood-pressure which is fairly constant does exist in cases of fibrillation, and that an approximate idea of the pressure conditions in the brachial artery can be obtained in the following way. The ordinary auscultatory method is employed, and two readings are obtained for both the systolic and diastolic blood-pressures. When measuring the systolic blood-pressure, the first reading is taken when the first sounds are heard as the pressure is reduced. The second reading of the manometer is taken when as many sounds are heard by the ear as pulsations are transmitted to the finger palpating the opposite radial artery. When measuring the diastolic blood-pressure, the first reading of the manometer is taken when pulsations of the opposite radial artery are not accompanied by corresponding sounds transmitted to the ear, and the second reading is taken when all sounds completely disappear.

VIII. *Urinary excretion.* The output of urine throughout each twenty-four-hour period has been recorded during the administration of the drug.

IX. *Clinical observations.* All the patients were kept under close clinical observation during and after their stay in hospital. Detailed records of alterations in physical signs were kept with special reference to changes in cardiac murmurs on the restoration of auricular function.

In cases of mitral stenosis the appearance, disappearance, or non-appearance of presystolic and diastolic murmurs at the mitral area has been carefully noted.

X. *Cardiac rhythm.* In all cases the cardiac rhythm has been investigated at frequent intervals by taking simultaneous radial and jugular tracings with the Mackenzie-Lewis polygraph.

V. *Case Records.*

Summaries of the clinical histories, treatment, and progress up to the time of writing of 20 cases of auricular fibrillation treated with quinidine will now be given. For convenience the cases are not reported in chronological order, but are classified into three groups, A, B, and C. Group A includes those cases in which quinidine has led to a return to normal sino-auricular rhythm which has persisted until the patient was discharged. Group B includes those cases in which only a transitory return to normal rhythm was effected, and in which relapse into fibrillation occurred prior to their discharge from hospital. Group C includes those cases in which quinidine has failed completely to exert this action. Group A is divided into two sub-groups, I and II. Sub-group I includes those cases in which auricular fibrillation has been of comparatively short duration, and which prior to the admission to hospital, during which they were submitted to the action of quinidine, had received no previous digitalis treatment. Sub-group II includes those cases in which fibrillation has been of comparatively long duration, and which prior to quinidine administration had received definite courses of digitalis therapy.

Group A. Sub-group I.

Case II. Female, aged 32, with rheumatic heart disease, mitral stenosis, and a history and signs of previous cerebral embolism. Duration of cardiac symptoms, 21 months. Duration of fibrillation, (?) 2 weeks. Admitted with acute heart failure, but digitalis treatment for 14 days partially restored compensation. Normal rhythm returned after 37 gr. had been administered over a period of 36 hours, with a maximum dosage of gr. viiss. eight-hourly. The only symptom of quinidine intoxication was sweating. The pulse-rate remained unchanged during quinidine administration and when normal rhythm was first restored. Subsequently there was a slight bradycardia which disappeared when the patient was allowed up, and since discharge the pulse has varied in rate between 70 and 90. A presystolic murmur appeared at the mitral area as soon as normal rhythm was restored, and a few days later an early diastolic murmur. When normal sino-auricular rhythm first returned the patient at once stated that she felt much better and that all palpitation of the heart had ceased, and objectively her general clinical condition seemed considerably improved.

Since discharge from hospital sino-auricular rhythm has persisted for 94 days without relapse. She has been able to climb stairs and do light work without dyspnoea, and has shown considerable improvement, and feels as well as she did a year before admission to hospital, when normal rhythm was probably present.

A case in which restoration of auricular function with quinidine at least maintained the same level of cardiac efficiency as digitalis first produced. But the general improvement in the clinical condition of the patient and the disappearance of signs of congestion following the return of normal heart mechanism rather suggest that cardiac efficiency had been raised to an even higher level. Moreover from a consideration of the patient's history and her field of cardiac response to exercise before and after quinidine treatment it seems probable that her cardiac efficiency had returned to its original level before the onset of auricular fibrillation.

Case VIII. Male, aged 62, with cardio-vascular degeneration, mitral incompetence, chronic bronchitis, and emphysema. Duration of cardiac symptoms, two years. Duration of auricular fibrillation indeterminate. Admitted with subacute heart failure, but digitalis treatment for five days restored compensation completely. Sino-auricular rhythm returned on the seventh day of quinidine administration after 110 gr. had been taken with a maximum dosage of gr. v six-hourly, when symptoms suggestive of arterial embolism occurred. Symptoms of quinidine intoxication were nausea and retching. The radial pulse-rate fell slightly during the latter stage of quinidine administration, but the rate remained slow and unchanged when normal cardiac rhythm was first restored. Subsequently it rose again to the pre-quinidine level, but a few days later a definite bradycardia appeared which persisted until after the patient was discharged, when the pulse-rate rose to a normal level. The urinary excretion was slightly increased after the restoration of auricular function.

When normal rhythm first returned there was no alteration in the subjective sensations or objective clinical condition of the patient. Subsequently the patient showed considerable improvement, but no more than could be attributed to natural recovery of the patient from the collapsed condition due to the occurrence of embolism.

Since discharge from hospital all physical signs of failure have remained absent, the patient has been able to return to light work, he only experiences dyspnoea on exertion, and now feels as well as he did one year before admission, i. e. one year after the onset of cardiac symptoms, the date of onset of fibrillation being indeterminate. Sino-auricular rhythm has now dominated the heart for 95 days and no relapse has occurred.

A case in which quinidine at least maintained the same level of cardiac efficiency as digitalis first established, but as the date of onset of fibrillation could not be determined, we do not know if the level of cardiac efficiency had been raised to its original level before the occurrence of this event.

Case IX. Female, aged 49, with rheumatic heart disease, mitral incompetence, chronic bronchitis, emphysema, and obesity. Duration of cardiac symptoms, nine weeks. Duration of fibrillation indeterminate, but probably nine weeks. Admitted with subacute heart failure, but digitalis treatment for nine days partially restored compensation. Normal rhythm was restored on the twelfth day of quinidine administration after 364 gr. had been taken with a maximum dosage of gr. xiv six-hourly, but digitalis was administered simultaneously with quinidine until sinus rhythm was established. Symptoms of quinidine intoxication were headache, diarrhoea, and visual changes. The pulse-rate rose with quinidine administration and the return to normal rhythm was preceded by a definite tachycardia, 100–120. When normal rhythm was first restored, the radial pulse-rate immediately dropped below 100, subsequently varied between 70–90, and after discharge from hospital between 90 and 100. The diastolic blood-pressure remained approximately constant, but the systolic blood-pressure fell during the tachycardia preceding the return to normal rhythm, but when this was restored the systolic blood-pressure rose to and remained at the pre-quinidine level. The urinary output was unaffected. There was no alteration in the subjective or objective condition of the patient when normal rhythm first returned. Subsequently there was distinct and steady improvement in the patient's general condition and she became much more active and less congested.

Since discharge from hospital she has continued to show definite clinical improvement, and states that she now feels as well and can do as much work as a year before admission, when according to her own statement cardiac symptoms only first appeared definitely nine weeks before she came into hospital. Normal rhythm has now been dominant for 44 days without relapse.

A case in which digitalis failed to restore cardiac compensation completely. The restoration of auricular function with quinidine not only maintained the same degree of cardiac efficiency as digitalis, but definitely raised it to a higher level. A consideration of the patient's history and the field of cardiac response to exercise before and after quinidine treatment suggests that cardiac efficiency had been restored to its original level prior to the onset of auricular fibrillation.

Case XI. Female, aged 26, with rheumatic heart disease, mitral stenosis and incompetence, and hyperthyroidism. Duration of cardiac symptoms, five months. Duration of fibrillation, indeterminate, ? four weeks or five months (see Fig. 1). Admitted with subacute heart failure, but digitalis treatment for sixteen days restored compensation completely. Normal sino-auricular rhythm (see Fig. 2) returned on the seventh day of quinidine administration after 128 gr. had been taken, with a maximum dosage of gr. viii six-hourly. Symptoms of quinidine intoxication were nausea, diarrhoea, and vomiting. The pulse-rate rose with the administration of quinidine and dropped to its normal pre-quinidine level, 70-80, when auricular function was restored. It remained at that level until the patient was discharged, since when it has varied round about 100. The diastolic blood-pressure remained constant, but the systolic blood-pressure fell slightly during the tachycardia preceding return to normal rhythm, but returned to its pre-quinidine level when normal rhythm was restored. Since discharge from hospital both the systolic and diastolic blood-pressures have risen slightly. The urinary output was not affected. When normal rhythm returned an early diastolic murmur gave place to continuous mitral mid-diastolic and presystolic murmurs. When normal rhythm was first restored there was no objective improvement in the patient's condition, but she spontaneously commented on complete disappearance of palpitation. Subsequently cyanosis completely disappeared and the 'hyperthyroidism' became much less pronounced.

Since discharge from hospital the condition of the patient has remained the same, and oedema of the feet has been present on one occasion. She still experiences dyspnoea on exertion, and does not yet feel as well as she did five months before admission to hospital, when cardiac symptoms first appeared, but considerably better than one month before admission, when auricular fibrillation probably first supervened. Sino-auricular rhythm has now been dominant for 71 days and no relapse into fibrillation has occurred.

A case in which restoration of auricular function has probably maintained the same level of cardiac efficiency as digitalis. The disappearance of cyanosis and the improvement in the hyperthyroid condition suggest that possibly cardiac efficiency has been raised to an even higher level. The date of onset of auricular fibrillation is not definitely known, and it is therefore impossible to say if cardiac efficiency had been raised to the same level as existed before the onset of this event.

Case XIII. Female, aged 59, with cardio-vascular degeneration, aortic incompetence, and exophthalmic goitre. Duration of cardiac symptoms, about three years. Duration of auricular fibrillation indeterminate. On admission she was well compensated, but digitalis treatment for 25 days failed to control the ventricular rate. The pulse became clinically regular for short periods on three occasions, but normal rhythm was not definitely restored until the ninth day of quinidine administration after 200 gr. had been taken, with a maximum dosage of gr. x six-hourly. Symptoms of quinidine intoxication were headache and diarrhoea. The pulse-rate, 100–110, after prolonged bromide and digitalis therapy fell steadily during quinidine administration to 60–70 and again slightly, and became much more constant when auricular function was first restored. Subsequently the pulse-rate rose again slightly and since discharge from hospital

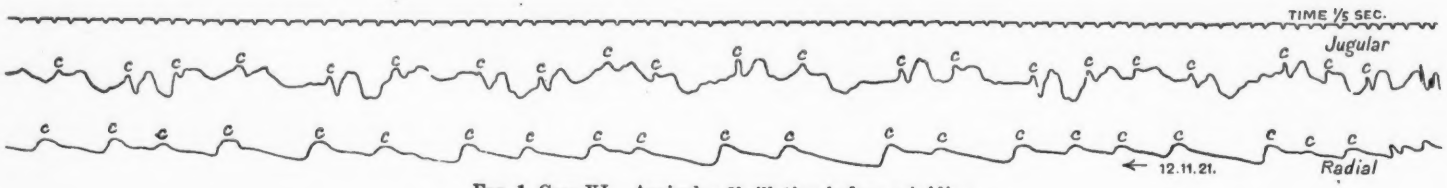

FIG. 1, Case XI. Auricular fibrillation before quinidine.

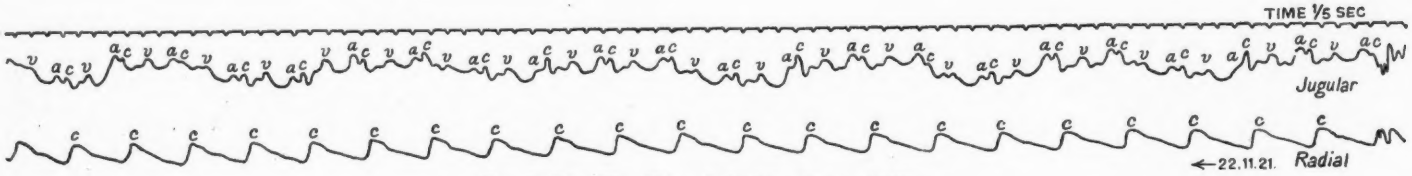

FIG. 2, Case XI. Normal rhythm after quinidine.

has varied between 80–90. The blood-pressures fell during the administration of quinidine, remained at a low level when normal rhythm returned, then rose again to their pre-quinidine level, and since discharge from hospital the systolic pressure has again risen slightly. The urinary output was definitely increased after sino-auricular rhythm was restored. When the dosage of quinidine was first reduced temporary relapse into fibrillation with fall of systolic blood-pressure occurred. The dosage was immediately increased and normal cardiac rhythm restored. When normal rhythm first returned there was no change in the objective or subjective clinical conditions of the patient, but subsequently she showed definite improvement in the thyroid condition.

Since discharge from hospital cardiac symptoms have remained absent, but the patient has been quite unable to do any work or walk about to any extent on account of a chronic tenosynovitis of both ankles, but there has been further improvement in the thyroid condition. Sino-auricular rhythm has now been dominant for 56 days and no relapse has yet occurred.

A case of exophthalmic goitre and auricular fibrillation with slight cardiac symptoms only, in which restoration of auricular function controlled the ventricular pulse-rate far more successfully than digitalis. When the patient was first admitted to hospital, signs of failure other than tachycardia were absent when she was resting in bed, and after discharge from hospital she was prevented from getting about and returning to a normal life by a chronic tenosynovitis.

Accordingly, apart from the questionable inferences that might be drawn from the radial pulse-rate, we have no evidence at present as to whether restoration of auricular function has raised cardiac efficiency to a higher level than digitalis, or if cardiac efficiency has returned to its original level prior to the onset of fibrillation.

Case XVII. Female, aged 30, with rheumatic heart disease, mitral stenosis, and incompetence. Duration of cardiac symptoms, six years, and fibrillation ? 14 months. Admitted with broncho-pneumonia and subacute failure, but digitalis treatment for twenty-one days restored compensation completely. Normal rhythm was restored on the fifth day of quinidine administration, when the dosage had reached a maximum of gr. vi six-hourly, and after a total quantity of gr. 78 had been taken. No symptoms of quinidine intoxication occurred. The blood-pressures, systolic and diastolic, fell slightly during the administration of the drug, remained low when normal rhythm was first restored, and rose again slightly when the dosage of the drug was reduced, but did not attain to their pre-quinidine levels. The radial pulse-rate remained unchanged during quinidine administration, when normal rhythm was first restored and subsequently. When normal rhythm was first restored a faint early diastolic murmur appeared at the mitral area and gradually increased in intensity. A mitral presystolic murmur only appeared later.

Since discharge from hospital she has remained well, the pulse remains normal in rate, all signs of failure remain absent, and she is now able to do as much work as she could three or four years ago.

A case in which digitalis restored compensation at rest in bed completely, but restoration of sino-auricular rhythm maintained the same level of cardiac efficiency as existed some time before the onset of auricular fibrillation.

Case XVIII. Female, aged 49, with exophthalmic goitre, auricular fibrillation, and myocardial failure. Duration of cardiac symptoms, six months, and of fibrillation indeterminate. On admission she was fairly well compensated at rest in bed, and treatment with digitalis and quinine hydrobromide led to considerable improvement in the thyroid condition but failed to control the ventricular rate. Normal rhythm was restored on the fourteenth day of quinidine

administration after 343 gr. of the drug had been taken with a maximum dosage of gr. xii six-hourly. The ventricular rate rose with the administration of the drug, fell abruptly to 80–90 when normal rhythm was restored, and rose to 90–100 when the patient was allowed up. The blood-pressure remained constant, but the output of urine showed a definite increase.

Soon after discharge from hospital the pulse-rate rose to 130 and symptoms and signs of failure returned without relapse into auricular fibrillation, but with considerable deterioration in the thyroid condition. Sino-auricular rhythm has now been dominant for thirty days, but is frequently interrupted by ventricular extra-systoles.

A case in which digitalis and rest in bed restored compensation completely, but restoration of normal rhythm while the patient was in hospital controlled the ventricular rate far more successfully than bromide and digitalis. When discharged from hospital tachycardia and symptoms and signs of failure reappeared, although relapse into fibrillation did not occur.

A case in which restoration of normal rhythm maintained the same or much more probably a lower level of cardiac efficiency than digitalis, and eventually did not control the ventricular rate any more successfully than, even if as well as, digitalis alone.

Case XX. Female, aged 48, with rheumatic heart disease, mitral stenosis, and incompetence, and a history of three previous embolic attacks. Admitted with acute heart failure, but six weeks' treatment with digitalis restored compensation completely. Duration of cardiac symptoms, eight years, and fibrillation probably eighteen months. Eighty gr. of quinidine with a maximum dosage of gr. vi six-hourly restored normal rhythm on the sixth day of treatment. A presystolic murmur returned at the mitral area and subsequently embolic infarction of the spleen occurred. The pulse-rate remained unchanged during quinidine administration, when normal rhythm was first restored, and subsequently. The systolic blood-pressure fell during quinidine administration and again when normal rhythm was first restored, but subsequently rose, but did not quite attain its pre-quinidine level. The output of urine remained unchanged.

Since discharge from hospital up to the time of writing sino-auricular rhythm has dominated the heart for twenty-three days, the pulse remains normal in rate, and all signs of failure remain absent. She now states that she feels as well as she did eighteen months before admission to hospital, when auricular fibrillation probably first supervened.

A case in which the restoration of sino-auricular rhythm with quinidine raised cardiac efficiency to the same level as existed immediately prior to the onset of auricular fibrillation.

Group A. Sub-group II.

Case I. Female, aged 58, with rheumatic heart disease, mitral stenosis, and incompetence. Duration of cardiac symptoms, eight years. History suggests three attacks of paroxysmal auricular fibrillation, and since the last, two and a half years ago, auricular fibrillation is known to have been constantly present. Well compensated on admission, having been treated with digitalis for two and a half years. Ninety-five gr. of quinidine administered in doses of gr. v eight-hourly caused return to normal rhythm on the sixth day of the treatment. Embolic infarction of kidney and lung occurred, quinidine was discontinued, and relapse into fibrillation was followed by embolism of the popliteal artery. A second course of quinidine produced tachycardia and auricular flutter, and 50 gr. of quinidine in doses of gr. v, thrice daily, produced a return to normal rhythm on the fifth day of administration. Except for one brief relapse preceded by auricular flutter the

pulse remained regular for forty-six days, when the patient stopped taking quinidine and experienced four attacks of paroxysmal auricular fibrillation. Quinidine, now administered as a prophylactic, produced auricular flutter, which digitalis converted into auricular fibrillation and then into normal rhythm with a transient attack of 1 : 3 heart-block. The pulse-rate rose with the administration of quinidine, and fell to its original level when normal rhythm was established. When relapse occurred when the patient was resting in bed there was no change in pulse-rate, but when relapse occurred when the patient was up and about a tachycardia supervened. The blood-pressure fell during auricular flutter. The urinary output was uninfluenced by return to normal rhythm.

A diastolic murmur appeared at the mitral area when normal rhythm was first restored and disappeared when relapse occurred. When normal rhythm was restored a second time mitral presystolic and diastolic murmurs both appeared. When normal cardiac rhythm first returned palpitation disappeared, but the objective clinical condition remained unchanged. When relapse occurred and the patient was in bed she experienced no symptoms, but when up and about symptoms and signs of failure supervened.

Up to the present time sino-auricular rhythm has dominated the heart for sixty-seven days, the pulse-rate remains normal, and all symptoms and signs of failure remain absent. She now feels better and able to do more than at any time during the last two and a half years prior to admission to hospital, when auricular fibrillation was present and the ventricular rate controlled with digitalis.

A case in which restoration of auricular function with quinidine has raised cardiac efficiency to a much higher level than digitalis alone, and approximately to the same level as before auricular fibrillation first established itself permanently.

Case III. Male, aged 36, with rheumatic heart disease, mitral stenosis and incompetence, aortic incompetence, and syphilitic infection. Duration of cardiac symptoms, two and a half years, and fibrillation at least two years. Admitted in acute failure, but two days of digitalis treatment restored compensation at rest completely. 150 gr. of quinidine with a maximum dosage of gr. x eight-hourly restored normal rhythm on the sixth day of this treatment, but embolic infarction of the spleen occurred. The pulse-rate rose with the administration of quinidine, dropped abruptly when normal rhythm was restored, when a bradycardia 40–50 persisted until the patient was allowed up. No presystolic murmur appeared at the mitral area and the urinary output remained unchanged.

Relapse into fibrillation occurred on the fortieth day of normal rhythm. When normal rhythm was first restored there was no alteration in the subjective or objective clinical conditions of the patient. When discharged from hospital the pulse-rate was normal and signs and symptoms of failure remained absent. When relapse occurred, signs and symptoms of failure supervened, but when the ventricular rate was controlled with digitalis the patient felt as well and could do as much as when first discharged from hospital with normal rhythm.

A case in which restoration of auricular function only maintained the same level of cardiac efficiency as digitalis, and probably did not raise it to its original level before the onset of auricular fibrillation.

Case IV. A female, aged 40, with rheumatic heart disease, mitral stenosis, and incompetence. Duration of cardiac symptoms, 19 years. Duration of fibrillation, one year proved, total duration indeterminate. Admitted with subacute failure, and digitalis treatment for 17 days partially restored compensation. 315 gr. of quinidine with a maximum dosage of gr. x eight-hourly caused return to normal rhythm on the eighteenth day of administration, but digitalis was given simultaneously with quinidine for nine out of the eighteen days. Symptoms of quinidine intoxication observed were sweating, diarrhoea, and abdominal pain. The pulse-rate rose slightly with quinidine administration, but the rise was checked with digitalis. When normal rhythm was restored a definite fall in

pulse-rate occurred and a bradycardia 50–60 persisted until the patient was allowed up, when the normal pulse-rate gradually returned. The urinary output was unaffected. Embolism did not occur. A presystolic murmur did not appear at the apex beat until some time after the patient was discharged from hospital. When normal rhythm was first restored there was no alteration in the subjective sensations of the patient, but objective clinical improvement was most definite and cyanosis and signs of venous congestion became much less marked.

After discharge from hospital, not only did the pulse-rate keep within normal limits, but cyanosis and congestion disappeared, and all signs of failure remained absent, and the patient herself stated that she had not felt as well or been able to do so much for the last seventeen years. She is now definitely far better than at any time when fibrillation could possibly have been present and the ventricular rate controlled with digitalis. Up to the present time normal rhythm has dominated the heart for 155 days and no relapse has yet occurred.

A case in which restoration of auricular function raised cardiac efficiency to a much higher level than digitalis alone, and the clinical improvement associated with the return of normal rhythm was really quite extraordinary.

Case VI. Male, aged 37, with cardio-vascular degeneration and mitral incompetence. Duration of cardiac symptoms, six months. Duration of fibrillation indeterminate, but known to be at least six months. Admitted with acute heart failure, but digitalis treatment for eight days restored compensation completely. 375 gr. of quinidine restored normal rhythm on the fifteenth day of treatment with a dosage of gr. x six-hourly, but one dose of Tinct. digitalis ♏xxx, was given two hours before normal rhythm was restored. Symptoms of quinidine intoxication observed were sweating, abdominal pain, and diarrhoea. The pulse-rate increased slightly with quinidine administration, and return to normal rhythm was associated with a slight fall in pulse-rate, followed two days later by a definite bradycardia, which persisted until the patient was allowed up and then gradually disappeared. The urinary excretion remained unchanged.

When normal sino-auricular rhythm was first restored there was no change in the subjective sensations of the patient and no immediate improvement in his clinical condition.

Since discharge he has also remained well, and signs of failure remain absent. He has returned to heavy work, which he accomplishes without dyspnoea, and now states that he feels better and can do more than at any time during the last six months prior to admission to hospital, when cardiac symptoms first appeared and fibrillation was present and the ventricular rate controlled with digitalis.

A case in which digitalis treatment raised the level of cardiac efficiency very considerably, but the restoration of auricular function seems to have raised it to a higher level still, and probably to what existed when auricular fibrillation first supervened.

Case X. Female, aged 30, with rheumatic heart disease, mitral stenosis and incompetence, aortic incompetence, and hyperthyroidism. Duration of cardiac symptoms, twenty-three years. Duration of fibrillation, one year (proved), but probably 14 months (see Fig. 3). Admitted with subacute heart failure, and digitalis treatment for eight days partially restored compensation. Quinidine was started in conjunction with digitalis, which was continued for three days only. Normal rhythm (see Fig. 4) was restored on the tenth day of quinidine administration, when the dosage had reached gr. xii six-hourly, and after a total quantity of 288 grains had been given, and intestinal embolism probably occurred. The only symptom of quinidine intoxication observed was headache. The blood-pressure fell slightly with quinidine administration and remained low after normal rhythm returned, but returned to normal when quinidine was discontinued.

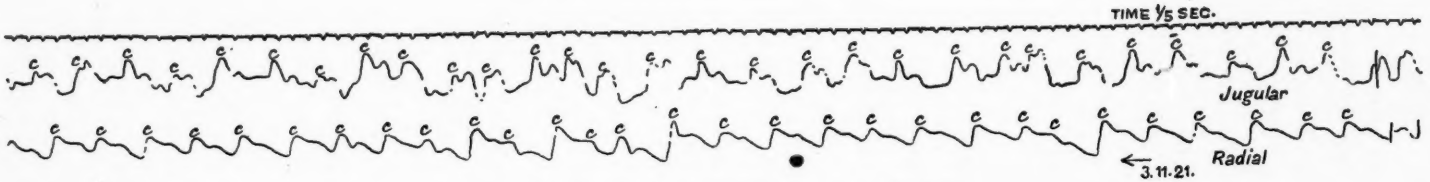

FIG. 3, Case X. Auricular fibrillation before quinidine.

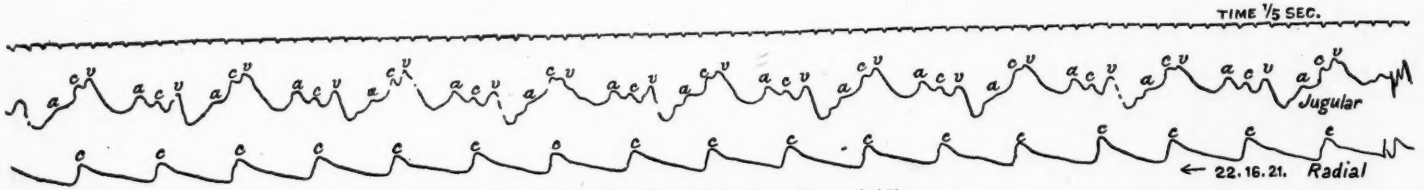

FIG. 4, Case X. Normal rhythm after quinidine.

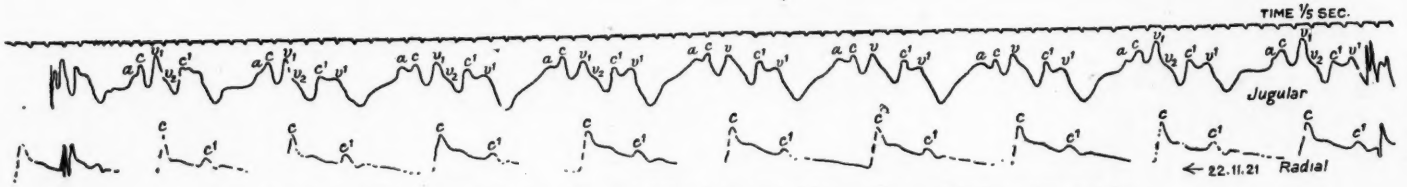

FIG. 5, Case X. Normal rhythm after quinidine interrupted by regular ventricular extra-systoles.

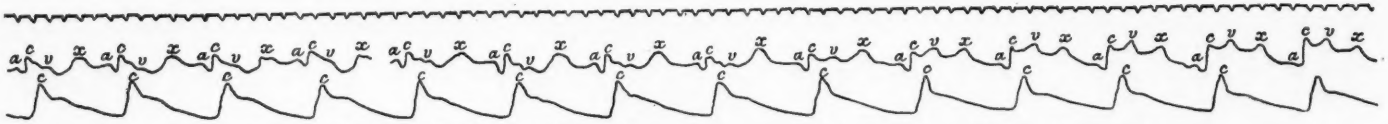

FIG. 6, Case X. Normal rhythm after quinidine interrupted by regular interpolated ventricular extra-systoles.

The pulse-rate remained practically constant, and the urinary output was unaffected by return to normal rhythm. When normal rhythm first returned it was frequently interrupted by regular ventricular extra-systoles, which occurred late in diastole after every ventricular beat, and were transmitted to the radial pulse so that the net pulse-rate remained unchanged (see Fig. 5). Quinidine was reduced and the extra-systoles occurred much less frequently, occurred earlier in diastole, and were too weak to be transmitted to the radial pulse, with the result that the pulse-rate at the wrist was halved. Quinidine was discontinued and the extra-systoles became still less frequent, occurred earlier in diastole, were too feeble to be transmitted to the radial pulse, and were now interpolated between successive normal radial beats (see Fig. 6), and occasionally between alternate beats (see Fig. 7) as the transition from the former to normal rhythm occurred. During the latter rhythm the extra-systoles fell a little later in diastole than when they were occurring interpolated between successive normal beats. The interpolated extra-systoles then disappeared altogether, but isolated auricular extra-systoles made their appearance. These isolated auricular extra-systoles often preceded short bouts of ventricular extra-systoles occurring late in diastole, causing the following normal beat to be missed but not being transmitted themselves to the radial pulse. As these auricular extra-systoles were considered possible danger signals of imminent relapse into auricular fibrillation quinidine was re-started as a prophylactic. When normal rhythm was first restored the mitral diastolic murmur disappeared and never returned. A mitral presystolic murmur did not appear.

When normal rhythm was first restored the patient commented on the disappearance of palpitation and stated that her heart was acting much more quietly. Subsequently there was distinct clinical improvement and cyanosis and congestion became much less.

After discharge from hospital the patient at first showed distinct clinical improvement, and cyanosis and congestion completely disappeared and natural colour returned to her cheeks. She was able to walk about gently and climb stairs slowly, but any exertion more than this led to dyspnoea.

Normal rhythm has now been dominant, though interrupted frequently by extra-systoles, and recently by short attacks of paroxysmal tachycardia for sixty-nine days, and in between the attacks the pulse-rate is within normal limits. Recently, however, she has not been so well, and cyanosis, congestion, and dyspnoea, even at rest, have returned, and the pulse has become more rapid.

A case of severe and probably progressive myocardial disease, which reacted fairly well to digitalis. Signs of congestion and cyanosis did not, however, completely disappear until normal rhythm was restored with quinidine. The patient's intelligence was not, however, sufficiently great to enable any comparison to be made between her condition when treated with digitalis prior to her admission to hospital for quinidine therapy and her condition after the restoration of auricular function.

Quinidine, however, at least maintained the same level of cardiac efficiency as digitalis first restored, and there is some evidence that for a short time it raised it to a higher level.

Case XIX. Female, aged 42, with rheumatic heart disease, mitral stenosis, and incompetence. Duration of cardiac symptoms, thirteen years, and auricular fibrillation, two months (see Fig. 8). Admitted with subacute heart failure, but digitalis treatment for seven days partially restored compensation. 40 gr. of quinidine with a maximum dosage of gr. v. six-hourly caused return to normal rhythm (see Fig. 10) on the third day of treatment, preceded by auricular flutter and varying degrees of heart-block (see Fig. 9). No symptoms of quinidine intoxication were observed. The radial pulse-rate (60–70) remained constant during quinidine administration, became twice as rapid when flutter supervened,

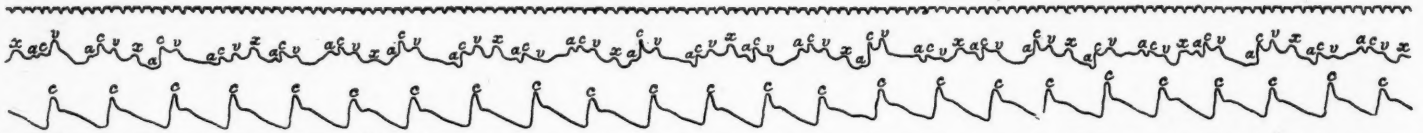

FIG. 7, Case X. Normal rhythm after quinidine interrupted by regular interpolated ventricular extra-systoles occurring after alternate normal ventricular beats.

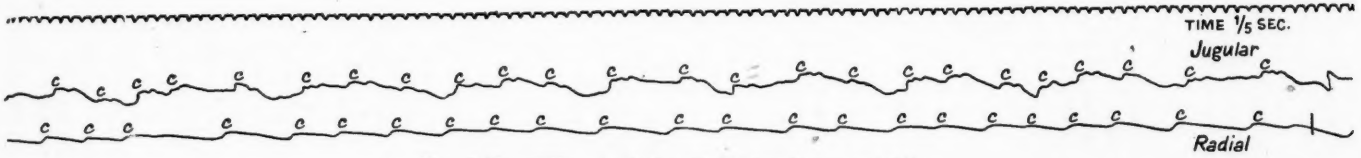

FIG. 8, Case XIX. Auricular fibrillation before quinidine.

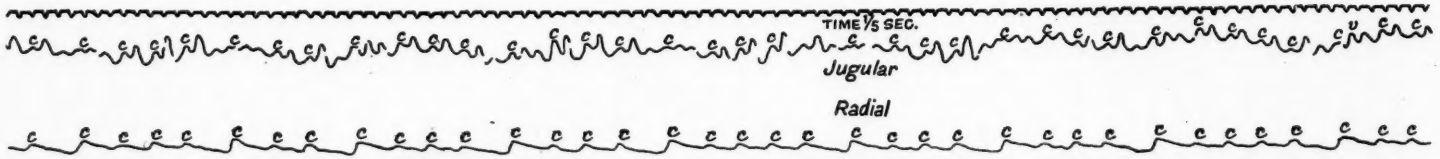

FIG. 9, Case XIX. Auricular flutter during quinidine administration.

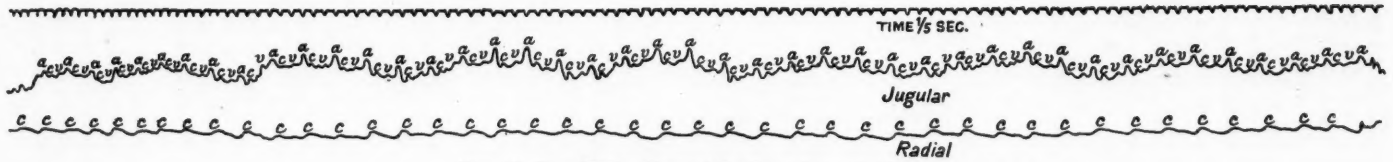

FIG. 10, Case XIX. Normal rhythm after quinidine.

and fell to 80–90 when auricular function was restored, and varied between 80 and 100. The diastolic blood-pressure remained constant, but the systolic fell with the onset of flutter and returned to its pre-quinidine level with onset of normal rhythm, and subsequently rose slightly. A mitral diastolic murmur was present at the mitral area when the auricles were fibrillating. When normal rhythm returned this murmur persisted and a presystolic murmur appeared.

When sino-auricular rhythm was first restored the patient noticed the disappearance of palpitation and said she felt much better and quite active. The cyanosis of the lips was less, but otherwise there was no objective change.

Since discharge from hospital normal rhythm has dominated the heart for twenty-three days, the pulse-rate has varied round about 100, and all signs and symptoms have remained absent. She now feels as well as she did some months before the onset of auricular fibrillation, and much better than at any time when the auricles were fibrillating and the ventricular rate controlled with digitalis.

A case in which digitalis failed to maintain compensation very successfully, but in which quinidine seems to have restored cardiac efficiency to a higher level than digitalis alone and probably to the original level which existed prior to the onset of auricular fibrillation.

Group B.

Case V. Female, aged 35, with rheumatic heart disease, mitral stenosis, and incompetence. Duration of cardiac symptoms, three years. Duration of auricular fibrillation indeterminate, but probably either twenty months or nine weeks. She was admitted with subacute heart failure, and digitalis treatment for two days restored compensation completely. 387 gr. of quinidine, with a maximum dosage of gr. x six-hourly, failed to restore normal rhythm on the eighteenth day of treatment. Digitalis was administered simultaneously on the last day of the quinidine course only. Symptoms of quinidine intoxication were diarrhoea, abdominal pain, profuse sweating, and a scarlatiniform rash. There was a slight rise in the radial pulse-rate. Digitalis was now administered for twenty-three days, when the second course of quinidine was commenced, the drug being administered in conjunction with digitalis, and on the fifth day of quinidine administration, after 75 grains in all had been taken, the pulse became regular and a presystolic murmur appeared at the mitral area. The objective and subjective conditions of the patient, the pulse-rate at the wrist, and the urinary output remained unchanged. The pulse-rate remained regular for three days, but relapse into fibrillation occurred when four doses of quinidine were omitted on account of headache. Relapse occurred without symptoms and without alteration in the pulse-rate. Quinidine was continued, and digitalis was now given simultaneously for five days, but on the twenty-sixth day of administration, when the dosage had reached a maximum of gr. xvi six-hourly, and a total quantity of grains 706 had been taken, the pulse was still irregular and the drug was discontinued on account of general deterioration in the condition of the patient. The pulse-rate remained unaltered. No definite symptoms of quinidine intoxication were observed.

The patient was discharged from hospital under digitalis therapy, considerably better than on admission, but still complaining of palpitation and shortness of breath on slight exertion.

Case XII. Male, aged 26, with subacute bacterial endocarditis occurring in a patient already the subject of rheumatic heart disease, mitral stenosis, mitral and aortic incompetence. Duration of cardiac symptoms, twenty-one months. Duration of fibrillation indeterminate. Admitted with subacute heart failure, and embolic infarction of lung occurred, but digitalis treatment for six weeks partially

restored compensation. Normal rhythm was restored after only 15 gr. had been given in doses of gr. v six-hourly, and sixteen hours after the administration of the first dose. Symptoms of quinidine intoxication were diarrhoea, vomiting, nausea, and anorexia. The dosage of quinidine was reduced and relapse occurred a few hours later. The pulse-rate remained unchanged during the administration of quinidine and when normal rhythm was first restored. When relapse into fibrillation occurred the pulse did not alter in rate. Subsequently a tachycardia developed.

The diastolic blood-pressure remained constant throughout, but the systolic blood-pressure fell slightly when normal rhythm was first restored and returned to its original level when relapse occurred. When normal rhythm returned the patient noticed the disappearance of palpitation, but there was no objective improvement. Relapse occurred without symptoms.

An interesting case from other points of view, but one that affords no evidence of the value of restoration of sino-auricular rhythm as a therapeutic measure.

Case XV. Female, aged 47, with rheumatic heart disease, mitral incompetence, and possibly some congenital defect. Duration of cardiac symptoms, four years. Duration of auricular fibrillation, twenty-six months. Admitted with subacute failure. Digitalis treatment for twelve days restored compensation completely. Normal rhythm was restored on the tenth day of quinidine administration after a total amount of 144 gr. had been given and when the dosage had reached gr. vii six-hourly. Shortly afterwards the patient had a sudden syncopal attack in which she almost died. Symptoms of quinidine intoxication were headache, nausea, diarrhoea, and vomiting. Relapse into fibrillation occurred with the attack, but normal rhythm reasserted itself spontaneously fourteen hours later in spite of the fact that quinidine had been discontinued. Quinidine gr. v, bis die, was then started, but relapse into fibrillation occurred twenty hours later without symptoms. The pulse-rate exhibited a slight increase during quinidine administration and a fall to its original level when normal rhythm was restored. When relapse occurred the radial pulse-rate was slightly increased, and remained constant when quinidine was discontinued. The blood-pressure, systolic and diastolic, fell slightly with quinidine administration, but recovered partially with restoration of normal rhythm. When relapse occurred the blood-pressure remained unchanged, and remained constant when quinidine was discontinued and did not return to its pre-quinidine level. The urinary excretion showed no change.

When normal rhythm was first restored the patient experienced relief from palpitation, but there was no objective change in her clinical condition.

During gradual recovery from the syncopal attack, relapse into fibrillation occurred without symptoms and without the reappearance of palpitation. In spite of this the patient showed progressive clinical improvement, became quite cheerful, and was thoroughly satisfied with the treatment she had received.

On being allowed up this clinical improvement persisted and she felt much better than on admission to hospital, but experienced shortness of breath on slight exertion and occasional attacks of cyanosis.

Group C.

Case VII. Female, aged 42, with rheumatic heart disease, mitral incompetence, and obesity. Duration of cardiac symptoms, eighteen months. Duration of auricular fibrillation indeterminate, but known to be at least a year. Fairly well compensated on admission. 450 gr. of quinidine with a maximum dosage of gr. viiss. eight-hourly had failed to restore normal rhythm on the twenty-second day of

this treatment. Two short courses of digitalis were given simultaneously with quinidine. The pulse-rate rose slightly with quinidine administration, but was checked rightly or wrongly with digitalis. The patient showed definite deterioration in the clinical condition and degree of compensation during the administration of quinidine. Symptoms of quinidine intoxication observed were sweating, abdominal pain, and diarrhoea.

Case XIV. Female, aged 23, with rheumatic heart disease, mitral stenosis, and incompetence. Duration of cardiac symptoms—haemoptysis, six and a half years; dyspnoea, &c., three months. Duration of fibrillation was known to be two, but was probably three months. Admitted with subacute heart failure, but digitalis treatment for four days restored compensation completely. 480 gr. of quinidine with a maximum dosage of gr. xv six-hourly failed to produce a return to normal cardiac rhythm on the thirteenth day of administration. The radial pulse-rate rose slightly, the blood-pressure remained constant, and the urinary output was slightly diminished. Symptoms of quinidine intoxication observed were headache, indistinctness of vision, abdominal pain, diarrhoea, and general malaise. Quinidine dosage was then reduced from gr. xv to gr. v six-hourly, and digitalis administered in conjunction with it for eight days, after which the dosage of quinidine was rapidly increased to gr. xii six-hourly. An additional 382 gr. of quinidine (making 862 gr. in all) on the twenty-sixth day of administration failed to produce a return to normal rhythm. The blood-pressure remained approximately constant. Owing to the simultaneous administration of digitalis, observations on pulse-rate and urinary excretion are of little value. Symptoms of quinidine intoxication observed, headache and indistinctness of vision.

Case XVI. Male, aged 51, with cardio-vascular degeneration, chronic bronchitis, and emphysema. Duration of cardiac symptoms, three years. Duration of fibrillation indeterminate. Admitted with subacute failure, but digitalis treatment for eight days restored compensation completely. 666 gr. of quinidine with a maximum dosage of gr. xviii six-hourly failed to restore normal cardiac rhythm on the sixteenth day of administration. Symptoms of quinidine intoxication were headache, dizziness, and visual symptoms. The blood-pressure, systolic and diastolic, fell slightly during the administration of quinidine and rose again when the drug was discontinued, but has not quite returned to its pre-quinidine level. The pulse-rate rose very slightly during the administration of quinidine, and subsequently returned to its original level. The urinary output showed no change.

VI. *Summary.*

A summary of the results obtained and the clinical observations recorded will now be given, and will be arranged so as to afford evidence towards the solution of the specific problems foreshadowed in Section I.

I. The percentage of unselected cases in which quinidine may be expected to restore sino-auricular rhythm.

Twenty unselected cases of auricular fibrillation admitted to the medical wards of a general hospital have been treated with quinidine, and in seventeen (85 per cent.) normal cardiac rhythm has returned. Of these seventeen successful cases, twelve were rheumatic, one rheumatic and infective, two degenerative, and two had auricular fibrillation associated with exophthalmic goitre.

Of the three unsuccessful cases, two were rheumatic, and one degenerative.

II. The best method of dosage of the drug.

A standard but arbitrary system of dosage has been adopted, and has not been departed from at present as the percentage of successful results is higher than that obtained by most previous workers. In all cases quinidine has been pushed to the maximum dose that it was thought safe to administer.

III. The relationship, if any, of the simultaneous administration of digitalis to the action of quinidine in restoring normal heart rhythm.

A. *The unsuccessful cases.*

The majority of the patients unless admitted well compensated were submitted to fairly long courses of digitalis prior to the first administration of quinidine. Two of the unsuccessful cases were admitted in decompensation, but were only treated with short courses of digitalis before quinidine treatment was instituted, i.e. Case XIV four days, Case XVI eight days. In both these cases the simultaneous administration of digitalis towards the end of the quinidine course failed to facilitate the action of the drug.

The third unsuccessful case (Case VII) was a patient with extreme obesity in whom compensation was only fairly good. During the administration of quinidine signs and symptoms of decompensation occurred and digitalis had to be administered.

B. *The successful cases.*

Of the successful cases digitalis was administered simultaneously throughout the quinidine course in Case IX; at the beginning of the course only in Case IV. The remaining cases, with the two following exceptions, received no digitalis simultaneously with quinidine. Case VI received one dose of digitalis on the fifteenth day of the quinidine course and two hours later normal rhythm returned. In Case V the administration of quinidine following a short course of digitalis (two days) failed to produce a return to normal rhythm. A second course of quinidine following a prolonged course of digitalis produced a transitory return to normal cardiac mechanism. A third course in conjunction with digitalis failed to produce any effect.

IV. The relationship, if any, of successful or unsuccessful quinidine administration and the dosage of the drug required to restore normal rhythm to the pathological condition of the heart.

Evidence on these points is furnished by the table on p. 311, in which the age and sex of the patient, the aetiological factors in the cardiac condition, the duration of cardiac symptoms in years, the probable duration of auricular fibrillation in months, the total amount of quinidine, the maximum dosage, and the number of days over which it was administered are put out in tabular form.

It will be seen that the minimum amount of quinidine which restored normal rhythm was in Case XII, a male with rheumatic heart disease and infective endocarditis. 15 gr. administered in 5 gr. doses six-hourly caused return to normal rhythm sixteen hours after administration of the first dose.

The maximum amount of quinidine which led to restoration of sino-auricular

rhythm was in Case VI, in whom 375 gr. produced a successful result on the fifteenth day. The maximum amount of quinidine given to any one patient without leading to a return of normal rhythm was in Case XIV, in whom 862 gr. with a maximum dosage of gr. xv six-hourly failed to exert any action by the twenty-sixth day.

V. The ill effects of administration of the drug,

A. *On the system generally.*

With the exception of those cases in which normal rhythm has been quickly restored certain symptoms of intoxication with quinidine have been the rule. Excessive sweating was a common complaint during the summer months. Mild gastric symptoms, nausea, anorexia, vomiting, abdominal pain, and diarrhoea, have been fairly common. Headache was frequent, and a papular scarlatiniform rash appeared in two cases. In the large majority of cases these symptoms passed off spontaneously without any reduction in the dosage of the drug. Visual symptoms, 'mistiness' of the eyes or transient attacks of loss of vision, were occasionally complained of during the administration of large doses of quinidine, and were usually associated with increased ventricular rate and fall of blood-pressure. Seeing that quinine is known to cause amblyopia, visual symptoms of moderate severity were always considered an absolute contra-indication against the further administration of quinidine. The continuous administration of quinidine gr. v, bis die, over long periods as a prophylactic, except in two patients who complained of chronic diarrhoea, did not lead to any untoward symptoms.

B. *On the heart itself.*

1. *Auricular flutter.* In the majority of cases the ventricular rate rose with the administration of quinidine, but no alteration in the cardiac rhythm was demonstrated. In a few cases the heart became 'more regular' and impure flutter was presumed to be present. In two cases only did pure auricular flutter probably occur. In Case I quinidine administered as a prophylactic to a patient in whom normal rhythm had previously been restored seemed to cause auricular flutter, which digitalis converted into auricular fibrillation and then into normal rhythm with a transient attack of 1 : 3 heart-block.

2. *Ventricular extra-systoles.* In Case X regular extra-systoles appeared, occurring after every normal beat when normal rhythm was first restored. As quinidine was reduced these extra-systoles occurred progressively earlier in diastole and eventually disappeared. In three cases isolated ventricular extra-systoles occurred when quinidine was being administered as a prophylactic (Cases VI, XVIII, and XX).

3. *Auricular extra-systoles.* Auricular extra-systoles never appeared immediately when normal rhythm was first restored, but occurred in several patients to whom quinidine was being administered as a prophylactic. In Cases I and XIII auricular extra-systoles preceded temporary relapse into fibrillation, and in Case X only appeared when quinidine was discontinued, and then preceded the appearance of attacks of paroxysmal tachycardia.

4. *Heart-block.* In only one case was return to normal cardiac rhythm associated with an a–c interval of greater length than 0·2 seconds. This occurred in Case XV, and followed a sudden syncopal attack in which the patient nearly died. The exact nature of the attack is unknown. But it seems more likely that the delayed conduction-time was due to the asphyxial conditions during the attack, than that the attack itself was due to acute heart-block. Possible causes of the attack were:

(a) Acute onset of auricular fibrillation;

(b) Embolism of a small branch of a coronary artery;

(c) Vagal stimulation;

(d) Ventricular fibrillation.

C. *Embolism.*

Embolism occurred definitely in three patients (Cases I, III, XX), and probably occurred in two others (Cases VIII and X). Of these five cases four had mitral stenosis, but in one only (Case XX) was there a history of previous embolic occurrences. In two other cases (VI, XII) there was a history of previous embolism, but when normal rhythm was restored embolism did not occur.

VI. The value of restoration of normal rhythm as a therapeutic measure and the possible relationship of this to the nature of the valvular lesion, and

VII. The relative value of (a) restoration of auricular function with quinidine, and (b) the control of ventricular rate with digitalis in the treatment of auricular fibrillation.

Of the fourteen cases in Group A it has been concluded that in thirteen the restoration of normal cardiac rhythm at least adequately maintained the same level of cardiac efficiency as digitalis first restored. In one patient only (Case XVIII), a case of auricular fibrillation and exophthalmic goitre, the procedure only maintained the same or more probably a lower level of cardiac efficiency than digitalis.

In eight of these first thirteen cases (Cases I, II, IV, VI, IX, X, XI, XIX) the restoration of sino-auricular rhythm probably raised cardiac efficiency to a higher level than digitalis alone. In six of these eight cases, again (Cases I, II, IV, VI, IX, XIX), cardiac efficiency was probably raised to the same level as existed before the onset of auricular fibrillation. Of the remaining two, in one (Case XI) the date of onset of auricular fibrillation could not be determined, and in the other (Case X) the patient's intelligence was such as to make it impossible for any comparison to be made.

In one case of the thirteen (Case III) the return of normal rhythm only maintained the same level of cardiac efficiency as digitalis, and did not restore it to the same level as existed prior to the onset of auricular fibrillation. An advanced degree of aortic incompetence was, however, present.

Of the four remaining cases of the thirteen, no comparison between the relative merits of quinidine and digitalis could be made because digitalis alone restored compensation completely, and these patients had received no digitalis prior to their admission to hospital for quinidine treatment. But of these four cases, in two (Cases XVII and XX) it was concluded that cardiac efficiency had

been restored to its original level prior to the onset of auricular fibrillation. Of the remaining two, in one (Case VII) the date of onset of auricular fibrillation could not be determined, and in the other (Case XIII) it was impossible to draw any conclusions owing to the presence of an intercurrent disease.

The particular patients in which clinical improvement was most striking were Cases I, II, IV, XVII, XIX, XX, in all of which mitral stenosis was diagnosed.

VIII. The contra-indications for the administration of quinidine.

In Case XV only did small doses of quinidine lead to excessive vomiting. The drug was pushed, and shortly after normal rhythm was established a syncopal attack occurred. It might possibly be suggested that this was a case of systemic intolerance of the drug.

IX. The effect on the blood-pressure, ventricular rate, and urinary excretion of (*a*) quinidine when the ventricles are fibrillating, (*b*) the restoration of normal rhythm, (*c*) quinidine after normal rhythm has returned.

A. Pulse-rate.

Except in those cases in which return of normal rhythm occurred very quickly, and with the exception of Case XIII, a patient with exophthalmic goitre in which a progressive fall in pulse-rate occurred, the administration of quinidine led to a progressive rise in ventricular rate. This rise was less noticeable in the three unsuccessful cases than in the cases in which normal rhythm was restored. In two cases auricular flutter with regular tachycardia was produced. When normal rhythm was suddenly restored, in the majority of cases an abrupt fall in pulse-rate occurred, but in a few there was no change. In five cases a definite bradycardia occurred which disappeared when the patient was allowed up. After discharge the radial pulse-rate usually remained within normal limits.

When relapse occurred when the patient was resting in bed, no change in pulse-rate occurred, but when up and about an irregular tachycardia supervened.

(*b*) *Blood-pressure.* The blood-pressure usually fell during the administration of quinidine, and the fall that occurred was usually associated with an increase in ventricular rate. When normal rhythm was restored the blood-pressure either remained unchanged or rose slightly. Subsequently the blood-pressure usually rose still further, but did not always return to the pre-quinidine level, and then remained fairly constant during the prophylactic administration of quinidine. The changes in the systolic were always more pronounced than changes in the diastolic blood-pressure.

(*c*) *Urinary excretion.* In only three cases was the restoration of auricular function followed by an increased urinary output (Cases VIII, IX, XVIII). In all the other cases the rate of urinary excretion remained unchanged.

X. The prognosis and tendency to relapse in those cases (*a*) if quinidine is discontinued, (*b*) if quinidine is continued indefinitely.

Of the three cases in Group B in which a transitory return to normal rhythm occurred, in Case V relapse occurred when four doses of the drug were omitted. In Case XII relapse occurred when the dosage of the drug was slightly reduced. In Case XV relapse occurred after the drug had been discontinued on account of

the syncopal attack which occurred, but when quinidine was again being administered.

Of the cases in Group A, in Case I relapse occurred frequently when the drug was discontinued during the early days of treatment. Lately, however, the patient has not taken quinidine, and normal rhythm has persisted up to the present time, i.e. sixty-seven days since the last relapse. Case XIII relapsed spontaneously while taking gr. v twelve-hourly, but gr. v eight-hourly has successfully maintained normal rhythm.

The remaining twelve have all taken gr. v twelve-hourly as a prophylactic, and in three cases only has relapse at present occurred. These three cases all exhibited exceptional features which the other cases did not. Case III was syphilitic and suffering from severe aortic incompetence. Case IX was a most unsatisfactory chronic alcoholic woman suffering from extreme obesity. Case X was the victim of severe and long-standing myocardial disease. Up to the present time the longest period over which normal rhythm has been maintained is 155 days.

XI. The effect of restoration of auricular function on the progress of coexisting disease with special reference to exophthalmic goitre.

Two cases (XIII and XVIII) of auricular fibrillation associated with exophthalmic goitre have been treated with quinidine. In Case XIII definite improvement in the hyperthyroid condition was recorded, and the return of normal cardiac mechanism controlled the ventricular rate far more successfully than bromide and digitalis. In Case XVIII no particular improvement in the thyroid condition was noticed, and although at first the restoration of normal rhythm undoubtedly controlled the ventricular rate more successfully than bromide and digitalis, when the patient was discharged from hospital a severe degree of tachycardia and symptoms and signs of failure reappeared without, however, any relapse into auricular fibrillation.

XII. Whether quinidine should be taken as a prophylactic against the onset of auricular fibrillation in patients suffering from certain forms of heart disease.

In Case I, after the return of normal cardiac rhythm, the patient stopped taking quinidine and experienced several attacks of paroxysmal auricular fibrillation which ceased to occur when she took quinidine. Little evidence has yet been accumulated, but it would seem logical to administer quinidine as a prophylactic to patients suffering from auricular fibrillation of the paroxysmal type, and also possibly to patients the victims of mitral stenosis and exophthalmic goitre, cases in which the incidence of auricular fibrillation is known to be exceptionally high.

Lastly, one or two interesting observations have been recorded which may eventually assist in throwing light on the pathogenesis of mitral presystolic and diastolic murmurs. Of the seventeen cases of auricular fibrillation in which normal rhythm has been restored, in eleven mitral stenosis was present. In eight out of these eleven cases mitral diastolic murmurs were present while the auricles were fibrillating. When normal rhythm was restored, in four the diastolic murmur

persisted and a mitral presystolic murmur at once made its appearance (Cases V, XI, XIX, XX). In one (Case IV) the diastolic murmur persisted and a presystolic murmur did not appear till some days later. In one (Case X) the mitral diastolic murmur at once disappeared and a presystolic murmur did not appear. In two (Cases III, XII) the mitral diastolic murmur persisted, but a presystolic murmur did not appear.

In the remaining three out of the eleven cases of mitral stenosis, mitral diastolic murmurs were absent while the auricles were fibrillating. Of these, in one (Case I) a diastolic murmur appeared at once when normal rhythm was restored, and disappeared when relapse occurred. When normal rhythm was again restored a presystolic murmur appeared at the mitral area, followed later by a diastolic murmur. In Case II a presystolic murmur appeared at once and was followed later by a diastolic murmur. In Case XVIII an early diastolic murmur appeared at once, but a presystolic murmur did not appear till considerably later.

It is interesting to note that the three cases in which mitral presystolic murmurs failed to appear when normal rhythm was restored (Cases III, XII, X) include Case III, in which the mitral diastolic disappeared with return of normal rhythm, and that all three of these showed incompetence of the aortic valves, and were the only three cases of the series in which aortic incompetence was diagnosed coexisting with mitral stenosis. This may only be a coincidence, but presumably in cases of aortic incompetence the diastolic intra-ventricular pressure is higher than in the normal heart with aortic valves intact. It is conceivable, therefore, that this increased pressure may successfully damp the vibrations which give rise to the mitral presystolic murmur during auricular systole, and thus prevent the appearance of this murmur in cases of mitral stenosis when aortic incompetence coexists.

In conclusion I would express my thanks to Dr. Charles Miller, Director of the Medical Unit, who has allowed me to take charge of all the cases of auricular fibrillation in the Unit wards. To Dr. A. W. M. Ellis, at whose suggestion this investigation was first undertaken, I am indebted for his constant interest and advice.

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TABLE (see p. 305).

	Group A.														Group B.			Group C.		
	Sub-group I.								Sub-group II.											
Case number	II	VIII	IX	XI	XIII	XVII	XVIII	XX	I	III	IV	VI	X	XIX	V	XII	XV	VII	XIV	XVI
Age	32	62	49	26	59	30	49	48	58	36	40	37	30	42	35	26	47	42	23	51
Sex	F	M	F	F	F	F	F	F	F	M	F	M	F	F	F	M	F	F	F	M
Aetiology	R	D	R	R	G	R	G	R	R	R	R	D	R	R	R	R I	R	R	R	D
Duration of cardiac symptoms in years	2	2	$\frac{1}{6}$	$\frac{1}{2}$	3	6	$\frac{1}{2}$	8	8	$2\frac{1}{2}$	19	$\frac{1}{2}$	23	13	3	2	4	$1\frac{1}{2}$	$6\frac{1}{2}$	3
Duration of fibrillation in months	$\frac{1}{2}$	?	?	?	?	14	6	18	30	24	24	6	14	2	?	?	26	1	3	?
Valvular lesions	M S M I	M I	M I	M S M I	A I	M S M I	Nil	M S M I	M S M I	M S M I A I	M S M I	M I	M S M I A I	M S M I	M S M I	M S M I A I	M I	M S	M S M I	Nil
Number of days previous digitalis treatment	14	5	9	16	25	21	56	42	700	2	17	8	8	7	23	42	12	Nil	4	8
Total amount of quinidine given in grains	37	110	364	128	200	78	348	80	95	150	315	375	288	40	75	15	144	450	862	666
Maximum dosage in grains	$7\frac{1}{2}$	5	14	8	10	6	12	6	5	10	10	10	12	5	5	5	7	$7\frac{1}{2}$	15	18
Number of days administered	$1\frac{1}{2}$	7	12	7	9	5	14	6	6	6	18	15	10	3	5	1	10	22	26	16

Aetiology. R = Rheumatic. D = Degenerative. G = Exophthalmic goitre. I = Infective.
Valvular lesions. M S = Mitral stenosis. M I = Mitral incompetence. A I = Aortic incompetence.

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QUINIDINE SULPHATE IN CARDIAC DISEASE

By JOHN HAY

With Plates 10–16

In October, 1921, Alan N. Drury and C. C. Iliescu published in the *British Medical Journal* their experience of the administration of quinidine sulphate in thirteen cases of fibrillation of the auricle, and stated that the number of cases so treated was well over 100. As an indication of the widespread interest in this matter I have been able to find records of 383 cases reported on by twenty-five observers, the majority of these having appeared since the publication of Drury and Iliescu's paper.

It is not difficult to understand the eagerness with which the problem is being investigated when one remembers that auricular fibrillation is present in over 60 per cent. of the cases of cardiac failure admitted into hospital, that it is often the cause of the acute cardiac collapse in the arterio-sclerotic with hypertension, and that it is not infrequently the explanation of the onset of rapid cardiac distress in patients suffering from mitral disease who, previous to the fibrillation, were endowed with adequate cardiac reserve.

Some experimental work by Eyster and Swarthout [1] on dogs has shown that fibrillation diminished the cardiac output by 40 per cent., and from the clinical evidence it is clear that the inception of fibrillation means a sudden and definite increase in the load which the heart has to bear.

Hearts with a liberal reserve may tolerate this sudden call with equanimity or they may rapidly compensate to meet it, but others with a narrower margin of reserve are overwhelmed, and the result is cardiac failure and a transitional period of stress. Under rest and medicinal treatment the fibrillation may be controlled and a condition of relative comfort produced, but at a lower level of physical effort than before.

Fibrillation being then so common an occurrence and also such a potent factor in the deterioration of a heart case, the appearance of a drug which, it is claimed, has the power to cut short this vicious arrhythmia is of the utmost importance, and it is essential that in so far as it is possible we should investigate its action and determine the indications and contra-indications for its exhibition.

It is possible by means of the electro-cardiograph to follow in detail certain important changes taking place in the heart in response to quinidine. These are definite and significant.

[1] *Archiv. of Int. Med.*, Chicago, 1920, xxv.

[Q. J. M., July, 1922.]

1. There is almost invariably a steady decrease in the number of auricular oscillations per minute, i.e. from 450 to 500 down to 250 to 300.

2. Occasionally auricular flutter appears with a 2 : 1 rhythm.

3. There is, as a rule, a steady increase of ventricular rate.

4. The appearance of ectopic beats, ventricular in origin, is common.

5. In about 50 per cent. of the cases the appearance of a normal rhythm.

6. Continuation of treatment with quinidine does not prevent the recurrence of the fibrillation.

My experience of quinidine sulphate is confined to fifteen cases. In twelve of these fibrillation was established and of some standing; in one it appeared towards the end of an attack of acute pneumonia; in another it was paroxysmal, and the remaining patient was suffering from paroxysmal tachycardia.

In six of the twelve established cases quinidine failed. Of these six one patient was so intolerant of the drug that it had to be discontinued after the first dose.

In three of the patients pure flutter developed. In one of the three this gave way to a normal rhythm, in another the flutter persisted after the quinidine was stopped, and in the third fibrillation returned while under treatment.

Of the seven in whom fibrillation was arrested it is too early to speak of the stability of the change, but in two, at least, there have been relapses. In four the improvement has been pronounced and the cardiac reserve has been considerably increased (see cases).

There was one death among the fifteen. This occurred in the patient suffering from paroxysmal tachycardia. It was most disappointing; the paroxysm had been cut short, and the patient appeared to be progressing satisfactorily when suddenly, without warning, she died. Death occurred twenty-four hours after the cessation of the abnormal rhythm and after 2 grm. of quinidine had been taken. No autopsy was permitted.

		Reverted to Normal.	Recovery only Temporary.	Flutter.	Total Failure to obtain Normal Rhythm.
Established fibrillation	(12)	6	2	1	6
Onset during pneumonia	(1)	1			
	(13)	7	2	1	6
Paroxysmal tachycardia	(1)	1	Died 24 hours later.		
Paroxysmal fibrillation	(1)		Ultimately much improved. Quinidine did not prevent recurrence of paroxysms. (See Plate 16, Fig. 8.)		

The usual procedure adopted has been as follows: The patient is kept in bed for a few days free from drugs. He is electro-cardiographed, and it is determined which of the three leads gives the most sharply-defined auricular oscillations, and this lead is utilized for observation. A tentative or experimental dose of 0·2 grm. quinidine sulphate is given, and all being well quinidine is started next day in full doses. An electro-cardiogram is taken twice a day when possible and any change noted in the action of the auricles and ventricles. In our experience the most satisfactory method of dosage is that of 2 grm. of the quinidine sulphate in the twenty-four hours given in capsules by the mouth, in doses

of 0·2 grm. for ten doses—given at 8 a.m., 10 a.m., 12 p.m., 2 p.m., 4 p.m., 6 p.m., 8 p.m., 12 a.m., 3 a.m., and 5 a.m. If necessary, the daily dose is increased to 3 grm. by doubling the dose at 10 a.m., 2 p.m., 6 p.m., 12 a.m., and 5 a.m. In the first few cases the dosage was 0·4 grm. at 8 a.m., 2 p.m., and 8 p.m., and sometimes another dose at 2 a.m.

The ward Sister has instructions that the heart is to be examined before each dose is given and the drug stopped if the action appears to be normal. As Sir Thomas Lewis has pointed out the action of the quinidine passes off rapidly, and it is desirable that there should not be any long delay between any two doses. The first six cases briefly recorded are those in which quinidine failed to procure a normal rhythm.

Case I. A. M., aged 24. Admitted 30.12.21. A case of old-standing valvular disease, rheumatic in origin. Mitral stenosis and regurgitation and slight aortic regurgitation. Marked distress for three years. Responds badly to digitalis. Is liable to attacks of decompensation, engorged liver, oedema, cyanosis, and severe dyspnoea. The preliminary dose of 0·2 grm. caused vomiting, headache, and feeling of considerable discomfort with orthopnoea. The ventricular rate ran up to 190, and the pulse became very feeble. It was not considered advisable to continue with the quinidine.

Case II. W., aged 36. Admitted 23.11.21. Moderate mitral stenosis and regurgitation with slight aortic regurgitation of old standing. Heart moderately enlarged. Presents the typical clinical picture of mitral disease. Dyspnoea on slight effort. Fibrillation probably dates back seventeen months (after the birth of her last child). Known duration since 23.8.21. Quinidine caused no discomfort, and there followed the typical slowing in the auricular oscillations (Plate 10, Fig. 1). A drop from 470 per minute to 300 with little, if any, change in the ventricular rate. Fibrillation persisted. Total quinidine 14 grm.

Case III. P., aged 46. Admitted 23.11.21. Mitral stenosis of old-standing, rheumatic in origin. Heart moderately enlarged ; no venous engorgement, always liable to rapid action. This was noticed for years before the fibrillation began. In June, 1920, there were short bouts of flutter. Fibrillation began November, 1920, and has persisted. Quinidine caused considerable distress, palpitation, giddiness, faintness, buzzing in the ears, and headaches.

The initial rate of the auricular oscillations was 480, with a ventricular rate of 150. The auricular oscillations fell to 320, and then, after 2·4 grm. of quinidine, flutter appeared with a 2 : 1 rhythm and an auricular rate of 240. This gradually increased to 288 next day. After 5·6 grm. fibrillation was resumed with an auricular rate of 405 ; this again fell, and after 7·6 grm. flutter reappeared. Auricular = 264, ventricular = 132. However, this again was transitory and passed into fibrillation with an auricular rate of 300 and a ventricular rate of 140. The auricular oscillations rapidly ran up to 450 on the cessation of quinidine. Total dosage 12 grm. See Plate 11, Figs. 2 and 3.

Case IV. B., aged 55. Admitted 6.12.21. A tall, pale man with an emphysematous chest, slight enlargement of the heart, no evidence of valvular disease. Blood-pressure not raised. Slight arterio-sclerosis. Fibrillation dates probably from 1917 ; certainly from August, 1921. The quinidine caused discomfort, chiefly headache and some praecordial pain. Before the administration of the quinidine the oscillations of the auricle were 450. The quinidine reduced the rate to 360. He had in all 12 grm. in doses of 0·4 grm. ter in die, but the fibrillation persisted.

Case V. W. J. B., aged 51. Admitted 22.2.22. A case of old-standing mitral disease, with definite enlargement, some limitation of reserve power shown by palpitation and shortness of breath. The aetiology is obscure, but he gives a history of syphilis, and the Wassermann is + +. There is no evidence of hypertension. The fibrillation is probably of some years' duration, but known to be present from June, 1921. There was practically no discomfort during the administration of quinidine. The usual rapid diminution in the number of the oscillations of the auricle took place. After 0·8 grm. they had fallen to 360, after 2·8 grm. to 260 per minute, and they remained at that level while the quinidine was being taken (Plate 12, Fig. 4). The outstanding feature was the steady development of the tendency to premature beats of various types. After 10 grm. the majority of the ventricular contractions were of this nature, and as the ventricular rate had risen from 92 to 138 per minute it was not considered advisable to continue with the quinidine.

Case VI. G. P., aged 36. Admitted 2.3.22. Heart enlarged. Mitral valvular disease. Evidence of very defective cardiac reserve. Marked emphysema. Probable duration of the fibrillation two years. Quinidine was begun on March 4, 1922, and produced some discomfort, slight palpitation and headache, nausea and buzzing in the ears. In all 10·8 grm. were given; 2 grm. daily in 0·2 grm. doses. An electro-cardiogram taken just after quinidine had been started showed a tendency to premature beats (Plate 13, Fig. 5 B). Fibrillation yielded to flutter, and the flutter showed a peculiar variation. At first the ventricular complexes were normal with a 2 : 1 rhythm; then a period ensued in which the ventricular complexes were similar to those of the premature beats above mentioned (Figs. 5 B and 5 D), and which had occurred before the inception of the flutter. These again suddenly gave place to flutter with normal ventricular complexes (Fig. 5 C). Owing to the discomfort and the refusal to respond the quinidine was discontinued. Later he was put on full doses of Tinct. digitalis without any material change in the rhythm. The injection of strophanthin sufficed to change the flutter into fibrillation with a rapid fall of ventricular rate to 80.

Case VII. D. R., aged 60. Admitted 12.12.21. Heart materially enlarged, but no definite evidence of valvular disease. Complained of praecordial pain and tenderness, and was conscious of the irregularity. Probable duration of fibrillation was five years—possible onset dating back to shell shock and exposure in the Dardanelles. Had been definitely observed since July, 1921. Transition from fibrillation to normal action was unnoticed by the patient. Took place after 1·2 grm. (Plate 14, Fig. 6). The rate of auricular oscillations when first observed was 408, with a ventricular rate of 84. Just previous to the transition the auricular rate was 360 and the ventricular 108. Normal rhythm started at 72.

Case VIII. E. W., aged 43. Admitted 6.2.22. Heart slightly enlarged, but no evidence of valvular disease. No venous engorgement. Some dyspnoea on exertion. Probable duration of fibrillation was twelve months. Tolerated the quinidine well. It caused some acceleration of the ventricular rate. Normal rhythm attained after 4·8 grm. There was marked improvement. He was returned to Pensions Hospital on February 18, 1922, and asked to be discharged to work March 2, 1922.

Case IX. W. A., aged 33. Admitted 18.2.22. Heart somewhat enlarged ($4\frac{3}{4}$ in. to left of mid-line). Suffering from valvular disease of rheumatic origin; aortic regurgitation and mitral regurgitation; no evidence of decompensation. Reserve power good. Probable duration one to two years. Practically no subjective symptoms, and nothing to suggest cardiac failure. Response to quinidine was rapid and satisfactory. Before quinidine, auricular oscillations were 480 per minute and ventricular rate was about 80 to 90. After 0·8 grm.

auricular oscillations were 420 and ventricular rate 72. After 2·8 grm. auricular oscillations had dropped to 330 and ventricular rate had risen to 110. The rhythm became normal after 4·2 grm., with cardiac rate of 90 and marked prolongation of the P. R. interval. No discomfort during administration of quinidine. 22.3.22: Two or three weeks after leaving hospital he noticed his heart suddenly become irregular. Normal for about ten days. Was never much distressed by fibrillation and is not distressed now.

Case X. P. B., aged 42. Admitted 18.2.22. Heart moderately enlarged. No clear evidence of valvular disease, chief complaint being palpitation and shortness of breath of two years' duration. Occasional dizziness and occasional slight praecordial pain. *Aetiology indefinite. Wassermann negative.* Duration of fibrillation probably two years. Known to be present from February 4, 1921. Ventricular rate 165 when record taken (Plate 15, Fig. 7). The average ventricular rate in bed was between 90 and 100. This was before the administration of quinidine. *Quinidine method of dosage.* 0·2 grm. in 10 doses every 24 hours at 8 a.m., 10 a.m., 12 p.m., 2 p.m., 4 p.m., 6 p.m., 8 p.m., 12 a.m., 3 a.m., and 5 a.m. to obtain continuity of effect. Only slight discomfort as result of quinidine. Occasional palpitation; steady rise in ventricular rate; slight headache and some buzzing in the ears. At 11.30 p.m. on February 23 he awoke and found his heart 'banging away'; about midnight it suddenly changed its rhythm. In this patient fibrillation changed to flutter after 2·4 grm., and after 2·8 grm. there was a 2 : 1 rhythm with the auricle beating at 270. After 3·4 grm. the rhythm became normal. This rapid ventricular rate did not appear to distress him materially. Four weeks after the restoration of a normal rhythm he felt better than for two years, and could walk up and down stairs with comfort.

Case XI. H., aged 42. Admitted 2.3.22. Definite enlargement of heart. Evidence of old-standing mitral disease (stenosis). No presystolic bruit. Duration of fibrillation probably eight years. Certainly 4½ years. Heart reverted to normal rhythm after 0·8 grm., and the presystolic murmur and thrill developed. Unfortunately, there were short relapses, during which the presystolic murmur and thrill disappeared.

Case XII. R. E., aged 39. Admitted 2.3.22. Heart enlarged. Apex beat 5th and 6th spaces. V.D.H. of old standing, dating from chorea when 20 years old. For last six years some dyspnoea on exertion. Symptoms worse since pneumonia last October. On admission cardiac reserve very poor. Considerable dyspnoea and palpitation on walking upstairs. 5.3.22: Heart reverted to normal action after 2·4 grm. Only slight symptoms of distress during the administration of quinidine. 10.3.22: The improvement was such that he was able to run up and down stairs without discomfort. 23.3.22: Improvement maintained. Later he reverted to fibrillation and was readmitted, and normal rhythm was restored after 2·4 grm. of quinidine.

Case XIII. Seen with Dr. Macalister and Dr. Murphy. I report this case although it was not possible to check the findings with the electro-cardiograph. Fibrillation occurred towards the latter end of a typical pneumonia in a healthy young adult of about 25. The temperature fell on the 6th day and fibrillation began on the 7th. The ventricular rate ran up to 160 and more beats per minute. Strophanthin intravenously had no effect, and the condition was causing very great anxiety. There was extreme dyspnoea and some cyanosis. Two doses of quinidine sulphate were given in 0·4 grm., which served to break the fibrillation, and recovery was uninterrupted.

Case XIV. A. C., aged 23. Well-nourished woman with slight thyroid enlargement. Liable to typical paroxysms of fibrillation. History indefinite as to date of first attack. Full doses of quinidine did not prevent the recurrence of fibrillation. During the periods of normal rhythm when quinidine was being administered it was found that the junctional tissues were depressed. See Plate 16, Fig. 8.

Later note, June 13, 1922. Through the kindness of the Editor it is possible to add further information concerning the after history of some of the cases recorded, thus bringing them up to date, and to give a very brief record of five additional patients who have been treated with quinidine sulphate.

Case VIII. Normal rhythm maintained.
Case IX. Has reverted to fibrillation.
Case X. Normal rhythm maintained.
Case XI. Refused intramuscular injections of calcium chloride and was discharged. Liable to recurrences of fibrillation.
Case XII. Normal rhythm maintained.

Of the five new cases the fibrillation yielded in each, but Case XV temporarily relapsed after some weeks. In this man a tendency to hydrothorax was materially lessened when the auricle resumed its normal activity.

Case XVIII is an example of the tendency to cerebral embolism on the cessation of fibrillation, a tendency present whether the cessation is spontaneous or induced. In this connexion, showing how easily quinidine may be blamed for untoward happenings, it might be well to record that a man aged 56 was about to be treated with quinidine, when, on the day he was to receive his first dose, he suddenly became blind from embolism of the cerebral artery of the retina in both eyes.

An attempt has been made with the later patients in the series to determine whether the administration of calcium chloride intramuscularly will stabilize the condition of the normal rhythm on the cessation of the fibrillation, but so far no conclusions appear to be justifiable.

Case XV. P. G., aged 51. Admitted 6.4.22. Case of arterio-sclerosis, with hypertension, and evidence of renal inadequacy. Mitral regurgitation present. Possibly syphilitic in origin. Some enlargement of the heart, engorged liver, no oedema. Fluid in the right pleura. 50 oz. withdrawn on April 14. On April 20 (third day of treatment) 36 oz. withdrawn from right chest. No further fluid collected. Probable duration of fibrillation, five years. Certain since April 6, 1922. Tolerated quinidine without discomfort. Complained of headache after 6·4 grm., at which point the rhythm became normal. Discharged May 13 feeling well, carrying his luggage down the stairs without loss of breath. After discharge there was a temporary relapse. On June 13 heart's action normal.

Case XVI. J. M., aged 30. Admitted 24.5.22. Mitral disease of old standing, moderate in degree. No venous engorgement. Heart slightly enlarged. Dyspnoea on exertion and palpitation. *Duration of fibrillation.* Probable seven years. Certain since May, 1922. Exhibition of quinidine caused no discomfort. Return to normal rhythm after 3·2 grm. on May 30. This was accompanied by the appearance of a soft diastolic bruit just internal to the left nipple. Intramuscular injections of calcium chloride, gr. 1 in ℥xx water, on May 31 and June 1, 2, 6, 9. Discharged 10.6.22. Normal rhythm maintained.

Case XVII. F. B. C., aged 32. Admitted 24.5.22. Mitral stenosis of old standing. Some enlargement. No bruits during fibrillation. Aetiology uncertain. Probable duration of fibrillation, seven years. Certain duration from February 16, 1921. No discomfort from quinidine. Normal rhythm after 1·6 grm. Half an hour after the last dose at 5 a.m. May 30 patient felt dizzy, 'drunk'. This lasted a few minutes, and when he recovered his pulse was found to be regular. With the resumption of normal rhythm a presystolic murmur developed and also a soft systolic murmur over the mitral area. After first tentative dose of 0·2 grm. at noon June 27 the ventricular rate increased from 90 to 115 at 10 p.m., and then dropped to 96 per minute. After the second tentative dose of 0·2 grm. given noon 28th the rate increased from 96 to 136 at 10 p.m., and then dropped to 88 by 10 a.m. Followed by intramuscular injections of calcium chloride, gr. 1 in ℥xx water, May 30, 31, June 1, 6, 9. Discharged 10.6.22 with normal rhythm.

Case II. *Mrs. W.* Mitral stenosis and regurgitation.
Slight aortic regurgitation.

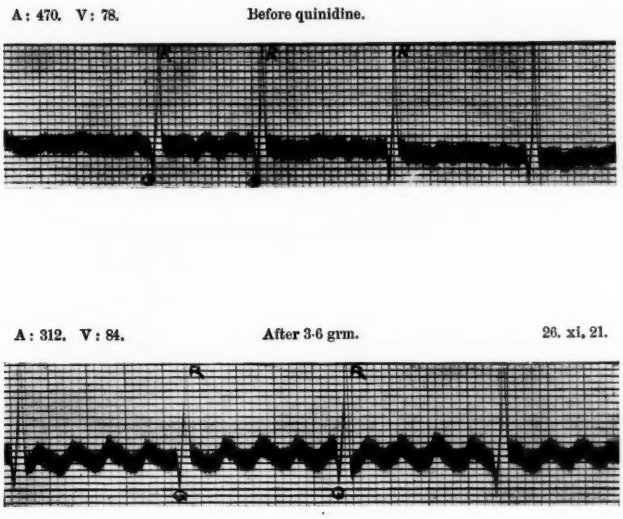


FIG. 1

Normal rhythm was not obtained.

Continued from p. 318:

Case XVIII. R. R., aged 37. 24.5.22. Double mitral lesion of old standing Heart enlarged 5 inches to left of mid-line. Aetiology uncertain. Wassermann positive. Cardiac reserve poor. Dyspnoea and dizziness and cardiac pain on exertion. Symptoms began suddenly November, 1914, since when he has never worked. Cannot tolerate digitalis. Quinidine caused discomfort, increase of dyspnoea, and headache. This persisted throughout treatment. Normal rhythm after 3·4 grm., May 30, 1922: No material change in subjective symptoms. June 4: Embolism, cerebral. Sudden, left-sided hemiplegia, hemianaesthesia, conjugate deviation to right, no loss of consciousness, no pyrexia. Still in hospital. Normal rhythm maintained.

Case XIX. C. H. W., aged 50. No clear evidence of any organic lesion of the heart. Spare, wiry man. There is some palpitation on exertion, shortness of breath, and an unpleasant sensation in the cardiac area. Fibrillation began May 19, 1922, following sprint of $\frac{3}{4}$ mile for a train. Seen on May 22. Heart rate 140, disorderly. Treatment with digitalis steadied and slowed the ventricles. General condition improved, but fibrillation persisted. On June 8, 0·2 grm. quinidine. On June 9, 0·2 grm. quinidine, followed in an hour by resumption of normal rhythm. Occasional ectopic beats auricular in origin. Ventricular action very slow. Normal rhythm maintained.

Case III. *Mrs. P.* Mitral stenosis.

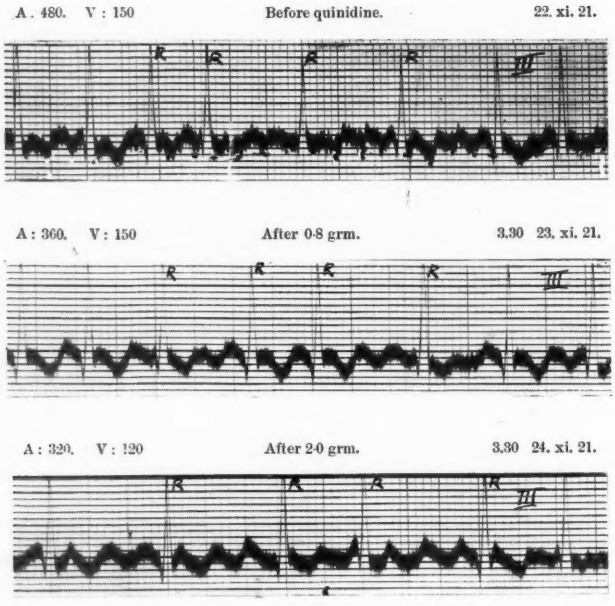


FIG. 2

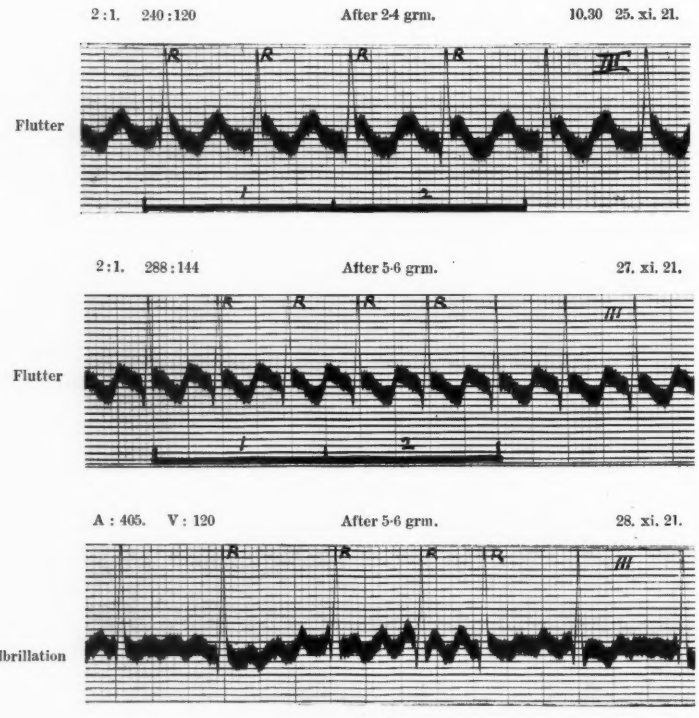
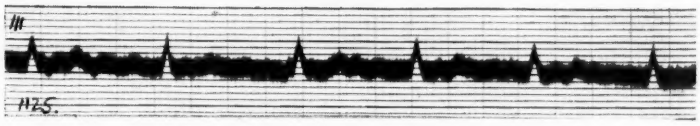


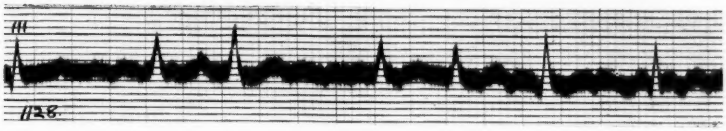
FIG. 3

Case V. *W. J. B., aged 51.* Large heart. Old standing mitral disease. Fibrillation known to be present since *June 1921.*

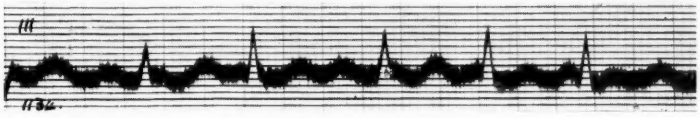
V : 92 After 0·4 grm. 10.30 a.m. 22. ii. 22.



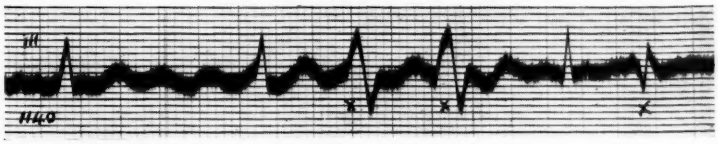
V : 108. A : 360 After 0·8 grm. 2.30 p.m. 22. ii. 22.



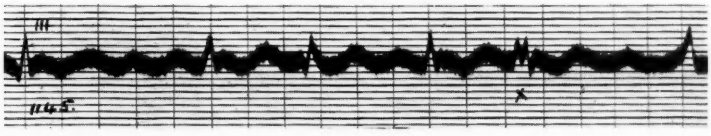
V : 100 A : 260 After 2·8 grm. 3 p.m. 23. ii. 22.



After 4·8 grm. 2.30 p.m. 24. ii. 22.



After 7.2 grm. 12·30 p.m. 26. ii. 22.



V : 138 After 0·0 grm. 10.30 a.m. 27. ii. 22.

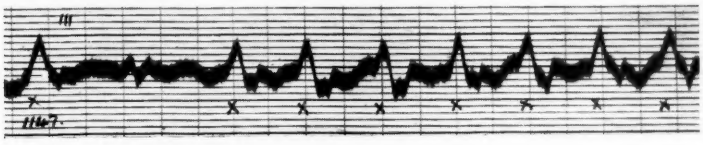
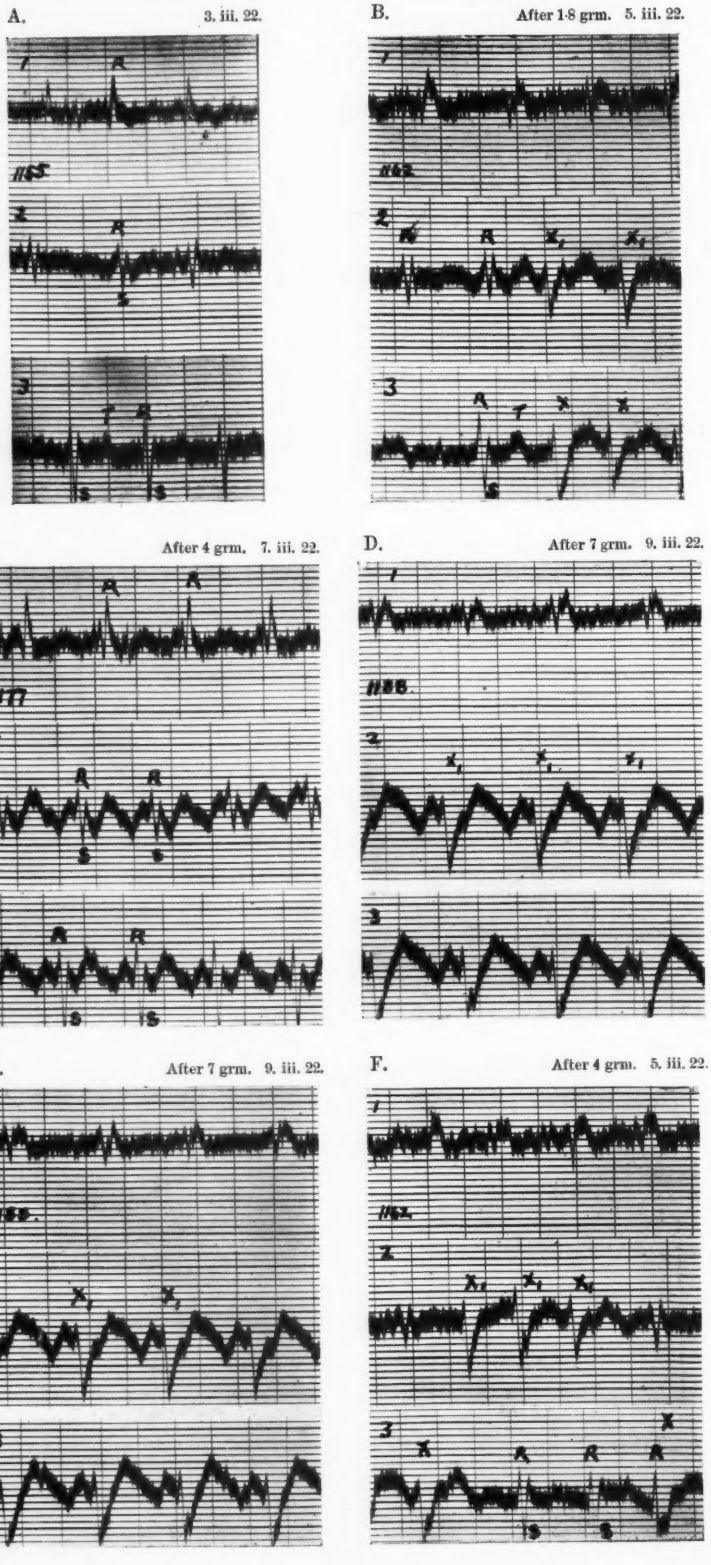


FIG. 4

x x Numerous ectopic beats excited by quinidine.



Case VI. *G. P.* Heart enlarged, very defective cardiac reserve.

A. Shows normal ventricular complexes.

B. Shows appearance of premature beats.

After 1·8 grm. Premature beats recorded **x**.

C. Shows 2:1 rhythm with normal ventricular complexes.

After 4 grm. Flutter 2:1 with normal ventricular complex.

D. Shows 2:1 rhythm with ventricular complexes similar to the premature beats in B.

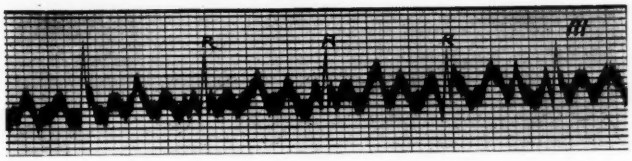
After 7·8 grm. Flutter persisting, but ventricular complex altered and is now comparable to premature beats **x** on 5. iii. 22.

E is the same as D, only it is placed with F to enable a comparison to be made between the ventricular complexes, F being the same as B.

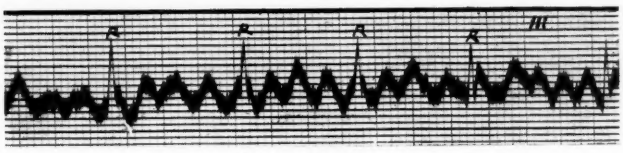
FIG. 5

Case VII. *D. R.* Heart enlarged, no V.D.H.

A : 408 V : 84 Before quinidine. 9. xii. 21.



A : 360. V : 84. After 3 grm. 12. xii. 21.



Normal 72. After 1·2 grm. 13. xii. 21.

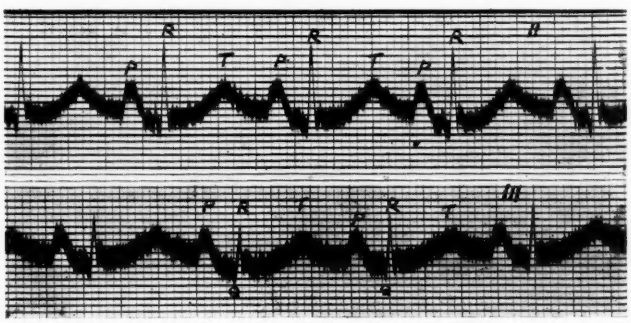
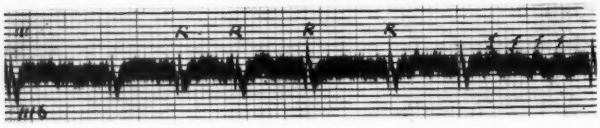


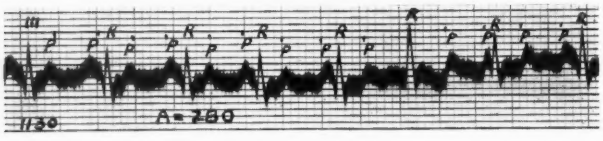
FIG. 6.

Case X. *P. B.*, aged 42. Mod. enlargement, no V.D.H.
Duration of fibrillation probably two years.

A : 510. V : 165 Before quinidine. 20. ii. 22.

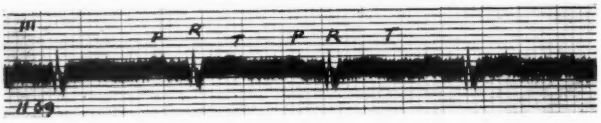


After 2·4 grm. 10,30 a.m. 23. ii. 22.



2 : 1 flutter. After 2·8 grm. 3 p.m. 23. ii. 22.

After 3·4 grm. 2.30 p.m. 24. ii. 22.



Rate 80 : Change to normal via flutter. 25. ii. 22.

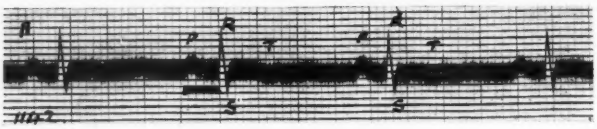


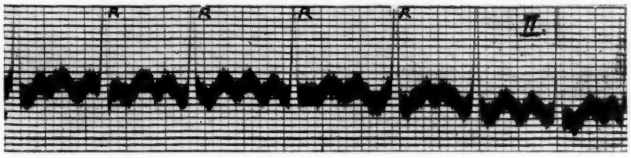
FIG. 7

Case XIV. *A. C.* No V.D.H.

Shows recurrence of fibrillation during the administration of quinidine sulphate.

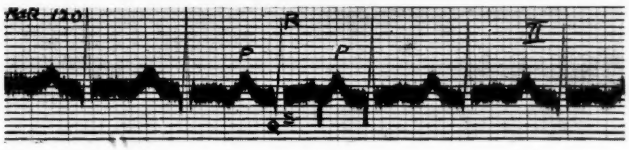
A : 420. V : 140. After 0·4 grm. 23. xi. 21.

Paroxysmal fibrillation

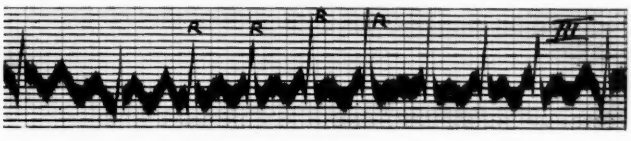


Normal rhythm but depression of conductivity. P R interval prolonged.

After 3·2 grm. 25 and 26. xi. 21.



Reverted. After 6·8 grm. 28. xi. 21.



Fibrillation which recurred while patient receiving quinidine.

Normal again. After 7·2 grm. 29. xi. 21.

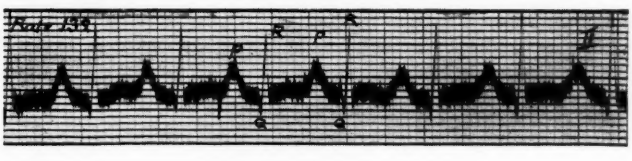


FIG. 8

ON CONGENITAL PORPHYRINURIA, ASSOCIATED WITH HYDROA AESTIVALE AND PINK TEETH

By LEONARD MACKEY and ARCHIBALD E. GARROD

With Plates 17 and 18

In the year 1892 McCall Anderson (1) described the cases of two brothers, aged 26 and 23 respectively, fishermen from the island of Lewis, who had suffered, from early childhood, from attacks of hydroa aestivale which recurred during each summer. The urine of the younger brother was persistently red, but that of the elder was said to be normal in colour during the intervals between the attacks of hydroa. Their skin was extensively scarred in regions exposed to light, and there was loss of substance of their ears and noses. F. Harris showed that the urine of both brothers owed its tint to a pigment of the haematoporphyrin group. Dr. Allan Cameron of Keose by Stornoway has been kind enough to obtain further information about these patients and their family. They were the third and fourth children of a family of seven, born of parents who were not blood-relations. The fifth child, a girl, died at the age of fifteen, and is reputed to have suffered from the same complaint, but on the death certificate is stated to have died of congenital cyanosis, chronic haematuria, and dropsy. The affected brothers died in 1900 and 1901 respectively, the elder of pulmonary tuberculosis and the younger of diarrhoea, whereas the four normal members of the family are alive and well.

The association of hydroa aestivale with haematoporphyrinuria, to which McCall Anderson was the first to call attention, has since been met with repeatedly, and it is hardly open to doubt that it was exemplified in two cases of earlier date, the one recorded by Schultz (2) and Baumstark (3) in 1874, and the other by Gagey (4) in 1896, although their inclusion in the list involves a revision of the original diagnoses.

Schultz's (2) patient was a man, aged 33, whose case was diagnosed, not without hesitation, as one of lepra bullosa, and from whose red urine Baumstark (3) obtained two abnormal pigments, one of which, uro-rubro-haematin, was undoubtedly a porphyrin. The description of the cutaneous lesions, and of the scarring and mutilations to which they gave rise, justifies a revised diagnosis of hydroa aestivale vel vacciniforme. Gagey's (4) patient, a boy of 14, suffered from his fourth year onwards from a skin eruption of a bullous kind confined

the age of four years. This may well have been a congenital case, but we have been unable to refer to the Danish original paper.

Where, as in this instance, we have to rely upon the statements of patients or their parents in dating the commencement of their malady it is naturally very difficult to determine which cases are and which are not congenital. Any one who has had experience with alcaptonuria cannot fail to have been surprised that persons who exhibit so conspicuous an urinary anomaly should live for many years without being conscious of their peculiarity, and it is difficult to justify the acceptance of cases in which hydroa is said to have developed during childhood and the exclusion of those in which its onset is dated from puberty or even later, such as Radaeli (15) describes. On the other hand, there can be no doubt that porphyrinuria is, in some instances, a symptom of acquired disease, and that if chronic it may give rise to hydroa. In a recent paper Günther (16) appears to lean to the view that an underlying diathesis renders some individuals specially liable to develop it, and this may explain its rare and capricious appearance among patients taking sulphonal.

In the present state of our knowledge we are certainly not justified in supposing that porphyrins are the only photo-sensitizing agents concerned in the causation of hydroa aestivale, although in its sex incidence, its onset in childhood as a rule, and its tendency to affect several members of a family, it resembles congenital porphyrinuria (17). In many hydroa records no mention is made of the urine, and in some no porphyrin was found, but in none of the cases have the faeces been examined from this point of view; so it may well be that the association of porphyrinuria with hydroa is more common than statistics indicate. In this connexion it should be noted that A. Perutz (18) has found that in some cases of hydroa in which the colour of the urine appears normal the chromogen of that pigment, which is, however, devoid of photo-sensitizing properties, is present in greater or less amount.

We have left to the last Günther's own case of congenital porphyrinuria, which is, at the same time, one of the most convincing, and that which has been submitted to the most thorough investigation. Upon Günther's study of it, and the later investigations of Hans Fischer and of Schumm, much of the knowledge of the subject which we possess is grounded.

The patient was a man, aged 33, who had passed red urine from early childhood, according to his statement from the second year of his life. From the age of 20 months he had suffered each summer from hydroa aestivale on his face, neck, and hands. There was the usual scarring, pigmentation, and mutilation of the ears and nose. The conjunctivae had been involved, and he had lost the sight of one eye. There were conspicuous deformities of the hands with fixation of joints and atrophy of the terminal phalanges. In the end his index fingers, which by their rigidity rendered his hands useless, were amputated, and the bones were found to be deeply pigmented as in Hegler and Fraenkel's case. A tooth which was extracted was of a yellowish-white colour, but the roots were found to be deeply stained, again as in the case of the bearded

woman. As time went on the spleen became enlarged, and it is noteworthy that gross enlargement of the spleen was a conspicuous feature in Schultz's case.

A very thorough chemical investigation was carried out by Hans Fischer (19), who showed that, despite their close spectroscopic resemblances, the abnormal pigments of the urine and faeces differed widely in their ultimate composition, and that both differed equally widely from the haematoporphyrin of Nencki, prepared by the action of powerful reagents upon haemin or haematin, as the following empirical formulae show:

Haematoporphyrin (Nencki)	$C_{34}H_{38}N_4O_6$.
Uroporphyrin (H. Fischer)	$C_{40}H_{36}N_4O_{16}$.
Stercoporphyrin (Fischer)	$C_{36}H_{36}N_4O_8$.

Fischer adduces strong evidence that stercoporphyrin (kotporphyrin) or a precursor thereof is first formed in the organism, and becomes, in part, converted into uroporphyrin (urinporphyrin) to facilitate its excretion in the urine. He showed, further, that the difference in formula of the two natural pigments is due to the fact that whereas the molecule of stercoporphyrin contains three, that of uroporphyrin contains seven carboxyl groups.

The close similarity of their spectra must be attributed to the presence, in all the members of the group, of a nucleus built up upon four pyrrol rings.

Schumm (20) has demonstrated slight differences of the positions of the absorption bands in the spectra of solutions of uniform acidity or alkalinity, by which the several porphyrins may be differentiated.

Observations on a trional urine by Ellinger and Riesser (21), and on a sulphonal urine by Schumm, render it highly probable that Fischer's results hold good for the porphyrins of urine and faeces generally.

In view of these findings it is better to speak of porphyrinuria than of haematoporphyrinuria, although we can hardly doubt that the metabolic porphyrins are derived from the blood-pigment.

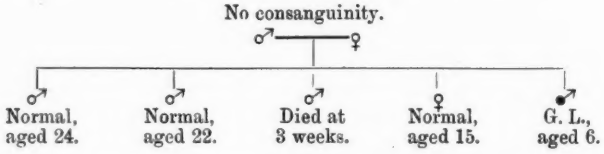
The remarkable experiments of Hausmann (22) and of Hans Fischer (23) upon animals, such as mice, and of Meyer-Betz (24) upon himself, show conclusively that the injection of haematoporphyrin, and of the natural porphyrins, renders the subjects highly sensitive to light, and we can hardly doubt that the presence of porphyrins in the tissues is the actual cause of the hydroa induced by exposure to light, and also of the toxic symptoms associated with acute porphyrinuria. On the other hand, we cannot ignore the evidence that in some cases the urine becomes darker in colour when the hydroa is active, and in some is said to have a normal colour in the intervals. Thorough examination of the urine in such cases is highly desirable, especially as regards the presence of the chromogen, porphyrinogen, seeing that light has the power of converting it into pigment, and the observations of Perutz, already referred to, suggest that it may play an important part in cases in which the porphyrinuria is apparently intermittent.

Fischer showed that whereas uroporphyrin is more potent in predisposing

to toxic symptoms, stercoporphyrin is chiefly responsible for sensitization of the superficial tissues to light, and he suggests that the symptoms vary according to the total and relative quantities of uro- and stercoporphyrin in the organism, which may determine the occurrence, in any given case, of cutaneous or toxic manifestations, or even of no complications at all. The detection of stercoporphyrin in the faeces is of special importance in cases of hydroa, and Günther's is the only case of congenital porphyrinuria on record which has been investigated from that point of view.

It is obvious from this sketch of the present state of our knowledge of this remarkable metabolic anomaly, that there are still wide gaps to be filled in, and that this can only be done by the investigation of fresh cases in the light of what is already known concerning congenital porphyrinuria. We are able, fortunately, to record such a case.

The patient, G. L., a boy aged 6 years, was born on May 6, 1916. He is the youngest of a family of five children. His mother was 40 years old at the time of his birth, and he is nine years younger than her fourth child.



The father, of Jewish descent, and the mother, of English parentage, are in good health, and know of no such anomaly in any member of their families. Consanguinity can be excluded.

Of their children the first, second, and fourth are alive and well, and present no abnormalities. The third child, a boy, was jaundiced from birth, and died at the age of 3 weeks, probably of atresia of the bile ducts.

The child G. L. was well formed and appeared quite healthy at birth, but his mother, who is an observant and excellent witness, is positive that the first urine which he ever passed was red and that it has been red ever since. The tint has varied from time to time, and has sometimes been brownish, 'like that of port wine'. She is also convinced that the faeces, although of normal appearance, stained the napkins red, apart from any admixture of urine, and has taken some trouble to obtain confirmation of these statements. She has never noticed any coloration of the sweat or saliva.

The infant was breast-fed, and nothing further was noticed until he was three months old, when, in August, 1916, a bullous eruption appeared upon his face and hands. It disappeared before the end of the year and left no scars. At nine months he cut his first tooth and it was pink.

The child was first seen by one of us (L. M.) in March, 1918, at the request of Dr. G. J. Dudley. At that time he had twelve teeth, all of a pinkish-red colour, hardly to be distinguished from that of the gums. His urine was limpid, of a ruby-red colour, and contained neither blood-pigment nor albumin. It

yielded no deposit when centrifugalized. Dr. L. C. S. Broughton, who kindly examined it, reported that the red colour was due to haematoporphyrin, and that the urine showed the characteristic spectrum of that pigment. The blood count was normal.

A careful clinical examination revealed nothing amiss beyond the abnormal colour of the teeth and urine. No scars were noticed upon the skin. The notes taken at that time state that there was no enlargement of the spleen or lymphatic glands, and that nothing amiss was discovered in the heart, lungs, abdomen, limbs or bones.

After an interval of three years the boy was again seen by both of us, when he was brought to a meeting of the Association of Physicians in Birmingham, and since then he has been under observation from time to time. He had grown into a bright intelligent boy, rather taller and heavier than Galton's averages for a boy of his age (height 43 inches, weight 43 pounds), but his face, knees, and backs of his hands were scarred. The colour of the teeth was still a most remarkable feature of the case, but their tint had undergone a change from coral pink to brown pink (Plate 17). His mother stated that during each spring and summer he had suffered from a severe skin disease which affected only the parts exposed to light. The active trouble ceased during the winter months, but indelible scars remained.

A fresh general examination showed nothing abnormal beyond the cutaneous lesions and the colour of the teeth and urine.

A blood count made in September, 1921, gave the following figures:

Red corpuscles	4,480,000
Haemoglobin	90 per cent.
Leucocytes	11,600
Polymorphonuclears	56 per cent.
Eosinophils	1 „
Small lymphocytes	38 „
Large lymphocytes	4 „
Large hyaline	1 „

The fragility of the red corpuscles was normal.

Dr. Douglas Heath, Dermatologist to the Birmingham General Hospital, who saw the boy at a time when the hydroa was active, has been good enough to furnish the following report on the condition of his skin:

'The patient is a rather thin and pale little boy, with very long black eyelashes and scanty hair. The skin of the whole body is of normal colour and texture, except where it has been exposed to light.

'On the uncovered parts of the body, i. e. the vertex of the scalp, the face, ears and neck, the extensor surfaces of the knees, and the backs of the hands, the whole of the skin is covered by recent and old scars which give the skin a wrinkled and lined appearance. The scarring is everywhere of a mild, soft type, and no cheloidal changes nor telangiectases can be seen. As might be expected the more recently scarred areas are pink, or faintly red, in colour, and

are more tense than the older ones. The eruption is, at present, most severe on the backs of the hands and fingers, so that the hands appear puffy and swollen as a whole, and independently of the local swelling due to the bullae (Plate 18).

'The eruption itself consists of:

'(1) Bullae, mainly from $\frac{1}{8}$ to $\frac{1}{2}$ an inch in diameter, with clear or faintly-red contents. These bullae seem to have no regular arrangement and are thickly or sparsely scattered over the affected parts. The great majority seem to be surrounded by unaffected skin, and show no areolae of redness. On the fingers and thumbs the bullae are extremely tense, and raised $\frac{1}{4}$ of an inch or so above the surrounding skin. Large bullae cover both thumbs, and the nail of the left thumb is raised from its bed. (The nails have been lost from time to time.) Similar but rather flatter bullae are scattered freely over the face, neck, ears, knees (fronts and sides), and also on the vertex of the scalp.

'(2) Purpura-like marks, from $\frac{1}{8}$ to $\frac{1}{2}$ inch in diameter, and of a purple-red colour which does not fade on pressure. These are abundant on the sides of the face and cheeks. They can be seen to follow the line of a slight scratch on the left cheek, and seem to occur after very slight injuries.

'(3) Excoriations, due to scratching, which very readily bleed. A very slight amount of friction seems to set up these sores. Several such excoriations can be seen on the vertex of the scalp and on the face.

'(4) Conglomerated milium-like epidermic cysts of a white colour which are closely set on many of the pink areas left after the bullae have dried up. These cysts are specially abundant upon the backs of the hands.'

Dr. Heath adds:

'Except for the fact that the eruption is confined entirely to the exposed surfaces of the body, and appears only in the summer months, it more closely resembles, in its clinical features, epidermolysis bullosa than hydroa aestivale. There appears to be in summer, in this patient, a vulnerability of the skin to slight injuries, but on the exposed surfaces only, a feature which is seen in a more widespread manner in epidermolysis bullosa. It appears that, when the skin has once been sensitized, external irritation, e.g. scratching, will keep up the eruption, as does further exposure to the sun.'

Cappelli, whose patient of the same age presented very similar lesions of the skin, writes in almost the same terms: 'Save for the strict limitation of the eruption to exposed parts, which has not been observed in all cases, the presence upon the backs of the hands, in addition to the usual secondary maculae and cicatricial depressions, of leuko-atrophic areas and of numerous miliform bodies, as also the slight dystrophies of the nails at times, might suggest a relationship between this affection of the skin and the so-called congenital pemphigus (= epidermolysis bullosa) with epidermic cysts.' Nevertheless, he expresses his conviction that the syndrome exhibited by his patient corresponds exactly to the rare and interesting skin disease to which Bazin assigned the name of hydroa vacciniforme.

Dr. Douglas Heath's observation of the contributory action of slight traumata constitutes, we believe, a new fact. It will be noticed that neither of the two children exhibits as yet any mutilation of the ears or nose.

The urine of our patient is limpid, has a ruby-red colour, and shows the four-banded spectrum of so-called alkaline porphyrins; so called because it is shown by solutions rendered acid by organic acids, and likewise by acid urines.

The addition to the urine of hydrochloric acid brings out the equally characteristic acid spectrum. Dr. E. A. Cockayne, who kindly examined a specimen with filtered ultra-violet rays, reported that the urine gave a rich red fluorescence, and that a very dilute solution, of a pale pink colour, obtained by the addition of a few drops of urine to water, showed a bright, ' old rose ' fluorescence.

In cases of porphyrinuria another abnormal pigment, or other pigments which yield no characteristic absorption bands, are present in addition to the porphyrin. Such pigment, the uro-fusco-haematin of Baumstark, is, in the experience of one of us, usually present in greater abundance in sulphonal urines than in the urine of non-toxic cases. In the case of G. L. the amount of such pigment is small, and when the porphyrin is precipitated by glacial acetic acid (Nebelthau's method) the filtrate has merely a brown tint of no great intensity. From the faeces also porphyrin is obtained in considerable quantity.

It is obviously of importance that the nature of the urinary and faecal pigments in this case should be thoroughly investigated upon the lines of Hans Fischer's work, and such an investigation is being carried out in the Laboratory of Organic Chemistry at Oxford by Mr. E. N. Allott, who will himself publish his results when the work is completed. We have his permission to state that the melting-points of the crystalline methyl-esters, of the urinary and faecal pigments respectively, leave practically no doubt that these are identical with the uroporphyrin and stercoporphyrin of Fischer.

The case here described affords the strongest evidence yet available of the existence of a truly congenital variety of porphyrinuria. The red colour of the urine at the first micturition, as to which we are ready to place reliance upon the statement of the mother, is of peculiar interest. There is good evidence that in cases of alcaptonuria the staining power of the urine is not noticeable until food has entered the alimentary canal, and in a case recorded by one of us (25) the mother, who had already borne an alcaptonuric child, and the nurse who attended her in both confinements, were on the look-out for the anomaly. Staining was absent fifteen hours after birth, the napkin removed twenty-nine hours after birth was slightly stained, and from fifty-two hours onward the staining was pronounced. Porphyrinuria, on the other hand, appears not to be influenced by diet, and it is worthy of note that there is reason to think that the porphyrin is an intermediate product between blood-pigment and bile-pigment, and it is present in the ante-natal meconium (26). The congenital onset in our case receives further confirmation from the very early onset of the hydroa, namely at three months.

It has been shown repeatedly that persistent porphyrinuria does not imply excessive blood destruction, and the blood count in this case lends further support to that view. It should be mentioned, however, that Schumm found haematin in the serum of Günther's patient.

Eosinophilia, which has been pronounced in some cases, and which is so common an accompaniment of bullous eruptions, is here lacking.

By far the most remarkable feature of our case is the colour of the teeth, which distinguishes it from all others hitherto reported. The pigmentation of the pulp in Günther's case, and in that of Hegler and Fraenkel, is, of course, a kindred phenomenon, but in those cases there was no discoloration of the enamel. Cappelli's is the only other case in which the milk-teeth have been present at the time of investigation, and it is inconceivable that so striking an appearance should have escaped the notice of so accurate an observer, who describes them as irregular, rather large, and with some erosion of the crowns.

Mr. J. Howard Mummery, to whom we appealed for information as to such coloration of teeth, mentions recorded cases in which a whole tooth has become diffused with a rosy tint, due to injury to the pulp and extravasation of blood, and the phenomenon known as 'pink spot' which results from chronic pulpitis. He also called our attention to cases briefly recorded by Thursfield and Langmead (27), in which children with persistent jaundice have shown a bright yellow, and later a green colour of the milk-teeth, a condition somewhat analogous to that seen in our porphyrin case.

Mr. Mummery thinks that the change of tint from bright pink to brown pink must rather be attributed to some change in the pigment than to increase of enamel after the teeth were cut. It seems possible that it may result from aggregation of the pigment into solid particles, for the solid pigment is brown in colour. We hope ere long, when the milk-teeth shall be shed, to have the opportunity of investigating the matter further, and it will be of great interest to see whether, in this case, there will be any similar coloration of the permanent teeth.

We have been able to satisfy ourselves, by a very simple method, that the bones of our patient are deeply pigmented also. When the hand of a normal individual is transilluminated by the light of an electric filament lamp the most conspicuous shadows are those of the large veins, whereas those of the bones are comparatively faint. But, when the hands of the patient were so transilluminated the shadows of the bones were dense, dark, and rod-like, but without any details of outlines. The appearances were quite different from those presented by the hands of two normal adults which were examined for purpose of control, and could only be explained by deep coloration of the child's phalangeal and metacarpal bones.

On the other hand, as might be expected, the bones, as shown in an X-ray picture, appeared of normal density. The radiogram brought out a further point of interest, viz. that ossification has been considerably delayed. The centres of ossification in the lower epiphyses of the ulnae, which should appear in the fourth year, were wholly absent; that of the trapezium was present in the right, but not in the left hand, and there was no sign of either scaphoid centre, although the examination was made only a few days before the boy's sixth birthday.

Summary.

We are able to record a fresh example of an extremely rare inborn error of metabolism.

In our case the evidence of congenital onset is more complete than in any recorded previously.

No other case of the anomaly is known to have occurred in the family of the patient, and his parents are not blood-relations.

The boy presents the usual association of porphyrinuria with extreme sensitiveness of the superficial tissues to light, as shown by annual eruptions of hydroa aestivale, vel vacciniforme, upon the exposed surfaces of his skin.

The case is quite exceptional in the deep pink coloration of the milk-teeth. The only other patient observed at so early an age showed no such colouration of his teeth.

Transillumination of the hands affords very strong evidence that the bones also are deeply pigmented. A radiogram shows that ossification of the carpal bones is delayed.

Porphyrins are present in the urine and faeces in considerable quantities. A chemical investigation is being carried out by Mr. E. N. Allott, who will publish his results when complete. So far as his investigations have gone, they indicate that the porphyrins present are the same as were found by Hans Fischer in the urine and faeces of another patient.

A *résumé* is given of the cases of congenital porphyrinuria previously described.

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AN INVESTIGATION OF THE BASAL METABOLISM IN UNSTABLE CONDITIONS OF CERTAIN ENDOCRINE GLANDS

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Introduction.

THE researches of Murray (1), McCarrison (2), Cushing (3), and many others have laid the foundations of our present knowledge of endocrine disorders. Particularly is this the case in conditions associated with the thyroid and pituitary glands.

Though much still remains to be discovered, the extreme grades of disordered function of these glands are now well recognized: the abnormal function may be one of excess or insufficiency.

In the case of the thyroid, a well-known group of symptoms has been collected and attributed to over-action of the gland. These syndromes are recognized in exophthalmic goitre and hyperthyroidism, while thyroid insufficiency is known to be the underlying factor in the production of myxoedema. Cretinism is its counterpart in childhood.

With regard to the pituitary gland, our knowledge is somewhat more scanty and perhaps not quite so well established. Clinical symptoms of over-action and insufficiency have been described by many observers, but we are chiefly indebted to Cushing and his collaborators for substantiating by experiment many views which had previously been largely a matter of conjecture. The work of Cushing has also added to our knowledge a good deal of new material in this branch of medicine. He adopts the view that pre-adolescent hyperpituitarism is likely to lead to gigantism, while the symptoms of acromegaly may supervene if the condition arises during adolescence or later. Insufficiency, on the other hand, is associated with the syndrome of infantilism, adiposity, drowsiness, a subnormal temperature, slow pulse and lowered metabolism, with under-development of the sexual functions.

That these glands play an important part in the regulation of body metabolism has long been realized, but it is only recently that the results of investigation of metabolism in abnormal conditions of the endocrine system have been generally applied in clinical medicine.

[Q. J. M., July, 1922.]

The gradual development of our present knowledge of this subject has been outlined by Du Bois (4). He has reviewed the early history of these investigations in the German literature. For the purposes of this paper an exhaustive *résumé* is not necessary, but some of the more noteworthy contributions will be mentioned.

Magnus-Levy (5) in 1895 was first to demonstrate an increase in metabolism in hyperthyroidism and a decrease in myxoedema. In 1909 Bergman (6) found a decrease in metabolism in myxoedema and an increase after thyroid administration.

Du Bois himself was the pioneer of metabolism investigations in this type of case in America. Later, Means and Aub (7, 8) emphasized the importance of basal metabolism determinations as an index of toxicity in hyperthyroidism. They also investigated the metabolism of patients with exophthalmic goitre before treatment, and for periods of two or more years after treatment. Boothby (9) and McCaskey (10) have supplemented this information, and laid stress on the value of basal metabolism determinations in clinical medicine. Various other investigations, chiefly in connexion with thyroid disease, have been published by Means and Aub (11), Boothby and Sandiford (12), Snell, Ford, and Rowntree (13), Means (14), Sandiford (15), Boothby (16, 17, 18), Mosenthal (19), Rowe (20), and Plummer (21). These papers deal with the various aspects of basal metabolism in thyroid disease. A few investigations have been carried out in pituitary disorders. Means (22, 23) investigated the basal metabolism in obesity, both of the simple and the pituitary type. Tierney (24) carried out further investigations into pituitary disorders, and his findings confirm those of Means. In cases of pituitary insufficiency subnormal basal metabolism readings were obtained. In simple obesity the basal metabolic rate was found to be unaltered. McKinley (25) investigated the effect of injections of extract of posterior lobe of pituitary on the basal metabolism in normal individuals and in those with endocrine disturbances. He found that the former responded quite constantly with a rise of metabolism, while his experiments in the latter group of cases suggested that pituitary extract was only effective in this way in the presence of a normally functioning thyroid gland.

Wiltshire (26) compared the basal metabolism during menstruation with that of the intermenstrual periods; no definite change was noted, but it was considered that the observations were insufficient to warrant the formation of a definite opinion. Observations of the basal metabolism during pregnancy are recorded by Baer (27).

In an investigation in 1918, Peabody, Wearn, and Tompkins (28) could find no evidence that the symptoms of 'irritable heart of soldiers' were at all related to hyperthyroidism.

Finally, the correlation of tests of sugar tolerance with basal metabolism determinations in hyperthyroidism has been investigated by McCaskey (29), and by Russell, Millett, and Bowen (30), who at the same time made observations on the adrenalin sensitivity of these cases. They concluded that the basal meta-

bolism test was the only functional test which invariably showed a positive response in cases of hyperthyroidism.

Outline of Present Investigation.

In the present investigation various estimations of basal metabolism have been carried out, both in conditions in which certain endocrine glands were obviously at fault, and in others in which, although some degree of glandular insufficiency was suspected, there was no clinical evidence pointing definitely to this conclusion. In the group of cases of the latter type with which this paper deals, the minor physical characteristics suggestive of glandular deficiency were frequently found associated with conditions which could be explained on the hypothesis that a loss of balance had occurred in the mechanism of the autonomic nervous system, the close relation of which with certain endocrine glands has frequently been commented upon.

The possible association of the condition of nocturnal enuresis with glandular insufficiency, more especially thyroid insufficiency, has frequently been suggested in the past, but no secure experimental evidence of this has been forthcoming. In the present paper it will be shown that many of these cases show definite evidence of a subnormal metabolic rate. This same feature is also seen in a wider group of cases with symptoms which could be referable to an over-excitability of the 'extended vagus', or parasympathetic division of the autonomic nervous system. This type of case has been described by Eppinger and Hess (31), and will be considered more fully in a later section of this paper. It will suffice here to emphasize in many of these cases the association of these symptoms with a subnormal metabolic rate. It appears, therefore, that, as normal metabolism is acknowledged to be largely dependent on endocrine activity, this diminished metabolism is of significance, and possibly suggests some degree of diminished glandular function in these conditions.

The Meaning of the Term 'Basal Metabolism'.

The degree of metabolism taking place in the body may be expressed in various ways. The simplest indication of this activity is the amount of heat given out by the body in a given time, and this heat production has frequently been measured by Benedict and others. Unfortunately, however, all direct methods of estimating the heat production are very expensive and complicated, and quite unsuitable for clinical work. It has been shown that accurate estimation of heat production can be determined in a simple manner by the indirect process of estimating the oxygen consumed. All clinical work on metabolism is now carried out on these lines.

Under ordinary conditions the body metabolism is not a constant factor, but varies with exercise and food. When the body is at rest and the patient starving, the influence of exercise and food is eliminated, and the heat produced

is then dependent on the fundamental processes of vital activity. This metabolism is fairly constant for different individuals under normal conditions, and is known as basal metabolism.

Methods of Estimating Basal Metabolism.

Various methods of indirect calorimetry have been employed from time to time. Benedict (32) has done a considerable amount of work on the comparison of these methods and in the establishment of normal standards. Lusk (33), Means and Woodwell (34), Blunt and Dye (35), have also published investigations dealing with this phase of the subject, while Talbot (36) has determined the standards of basal metabolism in normal infants and children.

The present investigations have been carried out by the Douglas bag method, as described by Cathcart (37). It is considered to be simpler, more accurate than other methods, and equally adaptable to all conditions. The experiment may be carried out at the bedside, the air analysis being completed in the laboratory.

The principle underlying the method is that, by the estimation of the oxygen consumed, and the carbon dioxide given off by the body in a given time, it is possible to calculate in calories the total heat production of the body per hour per square metre of body surface. These figures may be compared with normal standards. The results given in the present paper represent percentages above and below the normal. Briefly, the determinations are made in the following manner: A mouthpiece is adjusted to the patient's mouth, a clip to the nose, and by means of inspiratory and expiratory valves the total volume of expired air is collected in a Douglas bag over a period of ten minutes. After mixing well by kneading, this air is measured through an experimental gas meter, and a sample taken and analysed for its content of oxygen and carbon dioxide in a Haldane gas analysis apparatus. From these figures the total volume of oxygen consumed during the experiment can be deduced, and the caloric production calculated.

To eliminate the influence of exercise and food, the experiment is carried out after a preliminary period of twenty minutes' rest and twelve hours' starvation. In the present series of cases the patients have been investigated before breakfast after a period of twelve hours' starvation overnight. This entails little discomfort. It is essential to secure the co-operation of the patient, and to point out the need for complete muscular repose both during the preliminary period of rest and during the actual test. Any slight irregularity such as muscular movement or excitement will tend to raise the level of the reading obtained. For this reason it is suggested that the subnormal readings in this series of experiments are of especial significance, as many individuals show a tendency to breathe abnormally when the nose is clipped, while in the present series a considerable number of the patients were children, who are particularly susceptible to these influences.

The Thyroid Gland.

It has been definitely established that in conditions associated with thyroid over-activity the basal metabolism is considerably increased, whereas in states of insufficiency it is below the normal level. The general significance of these variations is fairly well understood, and it is realized that a knowledge of the basal metabolic rate provides valuable evidence as to the state of glandular activity prevailing at the time of observation; especially is this knowledge important as it has been repeatedly pointed out that conditions of hyper-activity may gradually merge into conditions of hypo-activity, the physical characteristics of hyper-activity being retained though the physiological functions of hypo-activity are present. A knowledge of the basal metabolism in such cases is of great value in clinical work.

TABLE I. *Types of Thyroid Disorders.*

	Sex.	Age.	Condition.	Duration of Illness.	B. M. R.	Subsequent Estimations.	Treatment.
1	F	47	Exophthalmic goitre	6 months	+72 %	(1) +47 % (2) +55 % (3) +46 % (4) +48 % (5) +46 % (6) +35 %	Rest, fat free diet, hemithyroidectomy
2	F	17	Exophthalmic goitre	1 year	+24 %	−1 %	Hemithyroidectomy
3	F	27	Exophthalmic goitre	4 years	+70 %	+39·4 %	Rest. Quinine hydrobromide
4	F	41	Hyperthyroidism	12 years	+28·6 %	+27 % −1·6 %	Hemithyroidectomy
5	F	42	Parenchymatous goitre	17 years	+1·6 %	+1·6 %	Hemithyroidectomy
6	F	41	Parenchymatous goitre	8 years	−1·6 %	−2·7 % +15 %	Thyroid extract
7	F	29	Simple adenoma	—	+5·4 %		
8	F	37	Adenoma	—	−30·4 % (3 months after hemithyroidectomy)		Thyroid extract
9	F	44	Toxic adenoma	4 years	+23 %	+20 % ±0 %	Hemithyroidectomy
10	F	7	Cretin	—	−19·7 % (on thyroid extract for years)		Thyroid extract
11	F	49	Myxoedema	—	−13·3 % (on thyroid extract)		Thyroid extract

In the diagnosis of doubtful cases, confirmatory evidence is obtained, while in those in which the nature of the condition is beyond doubt it is possible to estimate the degree of severity of the disorder. It can be seen, too, that a knowledge of the basal metabolism may be of great value in confirming the diagnosis of earlier and lesser grades of disturbed thyroid function, while in estimating the success of different forms of treatment, and in determining the fitness of convalescents to resume their occupations, its uses are obvious. In these cases information is obtained which is of great value in assessing the future capabilities of the patient.

A considerable number of cases of thyroid disorders of all types have been

investigated from this point of view. They include cases of exophthalmic goitre, hyperthyroidism, parenchymatous goitre, adenomata, myxoedema, and cretinism. The examples in Table I provide illustrations of these groups, and are selected with a view to demonstrating the value of a basal metabolism estimation.

(*a*) *Exophthalmic goitre.* The basal metabolism in cases of exophthalmic goitre is considerably above the normal level. The highest observation recorded in this series has been + 107 per cent. This represents a grade of extreme severity. Moderately severe grades show readings between + 60 per cent. and + 40 per cent., while the earlier and milder cases are below this level.

Three cases are taken as illustrations of this condition. Repeated estimations were carried out during the illness of Case 1, and these show the value of this test as an indication of the success of treatment. Although the condition was improved by rest and diet, the basal metabolism did not fall below + 46 per cent. after five months' treatment. Hemithyroidectomy was eventually performed, and the basal metabolism two months later proved to be + 35 per cent. At this point the patient considered herself fit to resume work. Clinically, she appeared well able to do this. Her pulse-rate had fallen from 118 to 80 per minute. The basal metabolism test showed, however, that hyperthyroidism was still present.

Case 2 illustrates the fall of the basal metabolic rate to normal after hemithyroidectomy. Case 3 had previously undergone two operations, respectively two years and one year before the present test which showed her basal metabolism to be + 70 per cent. above the normal. The second test, two and a half months later, showed the satisfactory results of rest and treatment with quinine hydrobromide. This treatment is being continued.

(*b*) *Hyperthyroidism.* Hyperthyroidism in this case was associated with the presence of a goitre, though toxic symptoms had only appeared during the last five months, following 'septic poisoning'. The goitre had been present for twelve years. The basal metabolism readings show the progress of the case. The patient gained nearly two stone in weight in the three months following hemithyroidectomy.

(*c*) *Parenchymatous goitre.* Case 5 appears to be a case of parenchymatous goitre with symptoms of neurasthenia—palpitations, nervousness, and suffocating feelings in the neck. Her pulse-rate fell from 119 to 90 during the course of the examination. Basal metabolism observations showed the absence of hyperthyroidism.

Case 6 had suffered from goitre for eight years, but for eight months had complained of weakness, palpitations, tachycardia, and tremor. It was suspected that she was suffering from hyperthyroidism. The result of the basal metabolism test showed that this was not the case, and suggested treatment with thyroid extract which proved to be successful. Graduated doses were given. Clinically, there was much improvement after the first fortnight's treatment, but up to this point the basal metabolism had not been raised. The dose was increased, and a further estimation of the basal metabolism showed the dosage necessary to maintain the normal level.

(*d*) *Adenoma of thyroid.* Case 7 proved to be a simple adenoma. The basal metabolism was within normal limits. This indicated that no extensive removal of gland was necessary.

Case 8 complained of great depression three months after the removal of a cystadenoma with part of the gland. The basal metabolism test proved the necessity of treatment with thyroid extract.

Case 9 illustrates the onset of toxic symptoms in an adenomatous condition of four years' duration. Nervousness and tremor with irregular menstruation had recently appeared. Rest and medicinal treatment failed to affect the basal metabolism, which only fell from + 23 per cent. to + 20 per cent. in three weeks, but two months after hemithyroidectomy the basal metabolism was normal. All symptoms had disappeared.

(*e*) *Cretinism and myxoedema.* In these conditions the basal metabolism is below the normal level. Cases 10 and 11, chosen to illustrate this point, had both been under treatment with thyroid extract for considerable periods. The test showed the need for increased dosage.

Puberty Goitres.

The value of basal metabolism estimations in such clearly-defined cases of thyroid disorder can easily be understood. But for those who are interested in tracing the beginnings of disease, the question arises as to whether this method of estimating thyroid function cannot be used to provide valuable indications of early loss of balance.

It is a common observation in the experience of every one that thyroid disorders frequently arise at one of the physiological epochs of life, especially if any conditions of stress are superadded. This is particularly noticeable in women where the endocrine system is more subject to wide variations of function and is consequently less stable. Abnormalities are frequently seen at puberty, during the menstrual periods, during pregnancy, and after childbirth, and particularly at the menopause.

It is suggested that an estimation of the basal metabolism in patients showing any tendency to instability at these periods will provide a valuable indication of any early abnormality, and enable suitable therapeutic measures to be adopted before gross alterations have taken place.

At puberty in many girls the thyroid gland enlarges. Frequently the condition is physiological and one of simple goitre, but in many cases there seem to be clinical features pointing to over-action. Change of temperament, malaise, loss of weight, tachycardia, palpitations, and attacks of faintness suggest the possibility of this condition. A fine tremor can frequently be provoked, and though no definite exophthalmos is present, the eyes often appear to be unduly prominent, and the palpebral fissures perhaps transiently wider than usual.

In a certain proportion of subjects, however, the opposite condition occurs. These patients frequently present many of the minor characteristics of thyroid

insufficiency described by Hertoghe (38). The skeleton may be undersized, the mentality dull. Such patients often have a characteristic puffy appearance; the skin is dry and rough, the hair coarse and lustreless and tends to fall out, the outer third of the eyebrow is scanty; further, the teeth are often irregular and carious, the nails furrowed, while the temperature of these patients is usually subnormal, their extremities are cold and cyanotic, and they tend to suffer with chilblains.

In many cases, however, of goitre appearing at puberty, features of both these conditions seem to be intermingled. The importance of recognizing the early stages of any loss of balance in all these cases is obvious, because it is at this period that equilibrium can most readily be restored and treatment rendered most effective.

The following series of five cases illustrates the points mentioned:

TABLE II. *Puberty Goitres.*

	Sex.	Age.	Condition.	Duration.	Features.	B. M. R.	Treatment.
1	F	17	Goitre hyperthyroidism	4 years	Anaemia, moist skin, flushes, tremor, pulse 112, dilated pupils, prominent eyes	+11 % +23 % +13·5 %	Hemithyroidectomy
2	F	12	Goitre hyperthyroidism	10 months	Pulse 115, dilated pupils, prominent eyes	+10·3 %	Quinine hydrobromide. Good result
3	F	16	Goitre hypopituitarism	6 months	Adiposity, constipation, headaches, irregular menstruation, dysmenorrhoea	−16·6 %	Thyroid extract. Good result
4	F	15	Goitre hypothyroidism	9 months	Loss of hair, headaches, fainting attacks, irregular menstruation, dysmenorrhoea	−14·9 %	Thyroid extract. Good result.
5	F	16	Simple goitre	6 months (marked), some years (slight)	Family history of goitre, home Wye Valley, goitrous district. Menstruation normal, excitable type	+7 %	Potassium iodide and Tinct. iodi.

Case 1 illustrates the onset of hyperthyroidism in spite of medical treatment. The basal metabolism rose from + 11 per cent. to + 23 per cent. in two months, at which stage it was considered that slight exophthalmos had definitely developed, and that the condition was one of early Graves's disease. Hemithyroidectomy was performed, and shortly afterwards the basal metabolism fell to + 13·5 per cent. with a marked improvement in all the clinical symptoms.

Case 2 is a similar case, but the condition improved and active symptoms subsided under treatment with quinine hydrobromide.

Cases 3 and 4 are examples of puberty goitre with glandular deficiency. In Case 3 the minor physical characteristics suggested a deficiency of pituitary origin, while in Case 4 the thyroid appeared to be at fault. In both cases the administration of thyroid extract relieved the condition; symptoms disappeared and normal menstruation was established.

Case 5 illustrates the type of simple goitre without any apparent glandular symptoms. The patient came from a goitrous district where many of the inhabitants suffered from goitre. In this case a slight goitre had been present for some years, but this had become considerably larger at puberty. The basal metabolism was + 7 per cent.

The Pituitary Body.

Determinations of the basal metabolism in disorders of the pituitary have not been made to anything like the same extent as in the case of the thyroid. This is probably due to the fact that the general features of these conditions, unless far advanced, are not nearly so readily recognized, and, owing to the obscure situation of this gland, alterations of structure are not apparent.

It has already been mentioned that Cushing adopts the view that pre-adolescent hyperpituitarism leads to gigantism, post-adolescent to acromegaly: whilst pre-adolescent hypopituitarism is seen in the syndrome of infantilism, adiposity, and the other conditions already enumerated. Further, if the insufficiency occurs after the period of growth is ended, similar states of adiposity and subnormal metabolism are likely to supervene. It is particularly in the case of the pituitary gland that Cushing calls attention to the mergence of states of hyper-activity into those of insufficiency, and he prefers to use the term dyspituitarism for disorders of the pituitary gland of this type owing to the frequent occurrence of features of both conditions. It is obvious that a knowledge of the basal metabolism is especially valuable in determining and treating the prevailing condition.

In the examples of acromegaly investigated in this series where the features of the disease are apparently progressive, the basal metabolism is above the normal, but an example is included in which a low reading is obtained. It is suggested that in this individual the gland is passing into a condition of insufficiency. In the examples of hypopituitarism the basal metabolism estimations are considerably below the normal level.

The following cases provide illustrations of these points: Cases 1 and 2 are advanced cases of acromegaly, with basal metabolism estimations above the normal. Case 3 has been already mentioned. In Case 4 the diagnosis was obviously uncertain, but it is included in the present series owing to certain suggestive physical characteristics.

Cases 5, 6, and 7 are typical of hypopituitarism, and conform to the features described by Frölich (39).

Cases 8 and 9 are of especial interest in that the minor physical characteristics of primary hypopituitarism are associated with premature development of the secondary sexual characteristics. This condition has been described by Horrax (40) as a polyglandular syndrome in which the symptomatology of a primary hypophysial disorder is associated with features suggestive of pineal implication.

TABLE III. *Pituitary Disorders.*

	Sex.	Age.	Condition.	Features.	B. M. R.
1	F	40	Acromegaly	Developed after confinement aged 23. Amenorrhoea since onset. Typical characteristics. X-ray: sella turcica much enlarged, terminal phalanges marked tufting	+25 %
2	M	35	Acromegaly	Characteristic features. Hands enormous. Prognathism. Violent headaches. X-ray: sella enlarged, characteristic tufting phalanges	+23 %
3	M	45	Acromegaly	Characteristic features. X-ray: sella enlarged, tufting phalanges. Headaches severe, pulse 48. ?Duodenal ulcer	−0·3 %
4	M	16	Dyspituitarism	Good health until influenza two years ago: now headaches, eye-aches, nervousness, giddiness, &c. Very coarse heavy features, very large hands (type en long de Marie), marked spacing teeth, upper and lower jaws. Abnormally hairy. X-ray, sella and fingers, nil	+37·7 %
5	F	9	Hypopituitarism, Frolich's syndrome	Typical. Subject to fits. Gained 2½ stone in last two years in spite of treatment with thyroid and pituitary extracts	−32·8 %
6	F	10	Hypopituitarism	Typical features. Adiposity, fine tapering fingers, &c. Optic atrophy	−33·3 %
7	M	15	Hypopituitarism, Frolich's syndrome	Typical adiposity of female type. Sexual infantilism: gradual onset 3–4 years. Sugar tolerance increased. Improved under thyroid treatment, but latterly put on weight again	−6·7 % (on thyroid extract)
8	F	13	Hypopituitarism	Premature secondary sexual characteristics. Otherwise typical features. Violent vomiting attacks controlled by whole gland pituitary extract	−23·6 %
9	F	14½	Hypopituitarism	Skeletal infantilism with premature secondary sexual characteristics. Treated with thyroid extract in large doses since age of four. Now improved on combination of thyroid and whole gland pituitary extracts	−14·1 %

In these advanced cases of hypopituitarism, the basal metabolism estimations are considerably below the normal level. Although this condition is encountered somewhat infrequently, the frequent appearance of individuals suffering from adiposity, amenorrhoea, or dysmenorrhoea, with minor physical characteristics suggestive of lesser grades of the same condition, is a common occurrence.

In contrast to the minor physical characteristics of thyroid insufficiency already enumerated, these individuals frequently present many of the features suggestive of pituitary insufficiency described by Cushing and others. The skeleton may be undersized, but adiposity is frequently present, and the mentality is bright and cheerful. The facies is characteristic, the features round, the cheeks full with pronounced malar flush, and the nose small with a broad bridge; the skin is smooth and velvety, the hair of the head fine and brittle and tends to come out. The hair of the rest of the body is frequently scanty. The teeth are usually good and regular, the nails small and thin, the extremities fine and tapering, especially noticeable in the fingers, although the hands are podgy.

Five cases are recorded in Table IV as examples of this type. The basal metabolism estimations are all subnormal, and it is noteworthy that these cases have been successfully treated with glandular extracts. These facts appear to be of significance when considered in conjunction with the results of basal metabolism investigations in the more obvious cases of hypopituitarism already described.

TABLE IV.

	Sex.	Age.	Features.	B.M.R.	Treatment.
1	F	43	Adiposity since birth of last child, increasing last 18 months. Dysmenorrhoea, scanty menstruation, constipation. Suggests hypopituitarism	−8·3%	Thyroid extract at first: slight effect. Hormotone afterwards: great improvement
2	F	13	Adiposity, debility. Suggests hypopituitarism	−9·1%	Thyroid extract: good result
3	F	16	Adiposity, debility, delayed puberty. Headaches. Menstruation established after three months' treatment	−6·3%	Thyroid extract: good result
4	M	31	Adiposity of female type. Excessive appetite. Lost 9 lb. in 14 days. Much fitter. Suggests hypopituitarism	(*a*) −10·4% (*b*) −2·8%	Thyroid extract: good result
5	M	19	Adiposity of female type. Debility. Suggests hypopituitarism	−9·3%	Thyroid extract: good result

Investigation of Similar Conditions with the Presence of Nervous Phenomena.

In the investigation of a series of cases such as those already considered it is impossible not to be impressed with the frequent occurrence of phenomena which could be attributed to disordered balance of the autonomic nervous system. The close connexion of certain endocrine glands with this system has long been recognized. This correlation is well seen in the case of the sympathetic system and the adrenals. Langley (41) and others have shown that the effect of adrenalin on any organ is the same as the stimulation of its sympathetic nerve. The sympathetic excites a secretion of adrenalin, and adrenalin increases the sensitiveness of the response to the sympathetic.

The thyroid gland is also considered to have close relation with the sympathetic system. Langdon Brown (42) has laid stress on this association and brought forward some evidence in its favour. Clinically the signs of over-excitability of this system are seen in Graves's disease.

It is rather, however, in connexion with phenomena perhaps attributable to parasympathetic over-excitability that this further investigation has been carried out. It is realized that symptoms which could be attributable to this source are seen in such conditions as Graves's disease, but it is not with these cases that the present paper deals, but rather with the occurrence of similar phenomena in patients in whom there is some reason to suspect some glandular deficiency. Where such a deficiency exists, it seems reasonable to suppose that a loss of tone would occur in the sympathetic system, and that, in these con-

ditions, sympathetic activity would be subnormal. From the results of basal metabolism investigations of the more obvious cases of endocrine deficiency it was considered likely that information of value might be obtained by similar methods of examination in these anomalous cases.

A series of twenty cases of nocturnal enuresis has been investigated from this point of view. The occurrence of this phenomenon in children suspected of glandular insufficiency and the value of treatment with thyroid extract have been described by Leonard Williams (43, 44) and others. This condition was chosen as a type for investigation owing to its occurrence in young subjects where the physical characteristics suggestive of endocrine deficiency are easily recognizable, and where little difficulty is found in obtaining accurate details of the complaint and in diagnosing and following various methods of treatment.

Many of the cases investigated present minor physical characteristics suggestive of endocrine deficiency, and in a large majority the basal metabolic rate is subnormal.

The following cases have been taken as illustrations of this series :

TABLE V. *Nocturnal Enuresis.*

	Sex.	Age.	Duration.	Frequency.	Onset.	Features.	B. M. R.	Result of Treatment.
1	M	13	7½ years	3 times per night	Followed appendicitis with appendicectomy	Small stature, puffy appearance, spade-like hands, eyebrow sign +; suggests hypothyroidism	−12 %	Thyroid extract. Cured
2	M	12	5 years	Every night	Followed scarlet fever	High-arched palate, eyebrow sign +. Headaches, night sweats, feels the cold; suggests hypothyroidism	−12·3 %	Thyroid extract. Greatly improved
3	M	12	11 months	3–4 nights a week	Followed scarlet fever	Coarse hair, puffy appearance, high-arched palate, frequent fainting attacks for last 6 months with profuse sweating; suggests hypothyroidism	−10·23 %	Now starting treatment with thyroid extract
4	M	13	5–6 years	Every night	—	Very small stature, eyebrow sign +, malar flush, velvety skin, podgy hands, tapering fingers; suggests hypopituitarism	−10·9 %	Greatly improved with thyroid extract
5	M	14½	10 years	Most nights	—	Typical hypopituitarism. Has been on thyroid extract for years. Controlled but not cured	+3·5 % (on thyroid extract)	On calcium lactate - ext. thyroid. No nocturnal enuresis for 2 months
6	M	13	2 years	Once a week	—	Sallow type. No suggestive minor physical characteristics	−13·1 %	Greatly improved on thyroid extract

The highest reading recorded in the complete series is +5 per cent. Very marked deviations from the normal, however, are not found, and it is not argued that too much importance should be attached to such results in any individual case. On the other hand, it is noteworthy that, in a series of cases such as the present, the basal metabolic rate is so consistently low that the figures obtained are probably due to some specific abnormality and can hardly depend on chance. The phenomena of nocturnal enuresis might be explained on the hypothesis that a loss of nervous balance occurs between the two subdivisions of the autonomic nervous system which control the functions of the bladder.

In discussing the innervation of the bladder and urethra, Pottenger (45) states that they carry with them the same innervation as the systems from which they are embryologically derived. The sphincters, that part of the bladder between the sphincters and the ureteral orifices known as the trigone, and the urethral musculature are activated by the sympathetics and inhibited by the parasympathetics. The body of the bladder is innervated in the same manner as the cloacal walls, activated by the parasympathetics, and inhibited by the sympathetics. Parasympathetic activity in this way produces emptying of the bladder.

Gaskell (46) has stated a generalization that when the sympathetic and parasympathetic divisions of this system are distributed to the same structure their effects are antagonistic. This has been confirmed by pharmacological tests.

In their monograph on vagotonia, Eppinger and Hess (47) have advanced the view that increased excitability of one system is accompanied by decreased excitability of the other. Langley considers that this view has not found much support.

It is suggested, however, that in this series of cases of nocturnal enuresis, where a subnormal metabolic rate is suggestive of some endocrine deficiency, a decreased excitability of the sympathetic division is present with a relatively increased excitability of the parasympathetic division. In the latter system, the threshold of stimulus would be lowered. Consequently stimuli which normally should result in a balanced reaction would tend to produce phenomena of parasympathetic overaction; i. e. irregular emptying of the bladder. Any local reflex source of irritation would tend to exaggerate this tendency.

An additional point is of great interest. There is a considerable amount of evidence to support the view that sympathetic activity is intimately associated with the ordinary emotional states of everyday life. It is suggestive then that evidence of loss of balance appears at night when these stimuli are not present, and when sympathetic activity is still further depressed, the balance being restored during the day when this system is again stimulated. Hence, the infrequency of bladder symptoms in these children during the daytime.

This hypothesis appears to be further strengthened when the development of the autonomic nervous system is taken into account, for Langley (48) has pointed out that the parasympathetic is phylogenetically of earlier origin than

the sympathetic. It is a generally recognized scientific truth that the faculty most recently acquired is the first to be suppressed in times of stress. It is suggested that under these circumstances stress is more likely to fall on the sympathetic endocrine system, which will tend to lose its tone.

TABLE VI.

	Sex.	Age.	Duration of Illness.	Features.	B. M. R.	Subsequent B. M. R.	Treatment.
1	M	49	12 years	*Intestinal symptoms predominating.* Wakes up at 3 every night with colic and wind + + +, spastic colon. Visceroptosis examination kidneys, X-ray, &c. nil. Followed motor accident with concussion 1909	−5 %, but took hormotone for previous 4 days	−17 %	Thyroid extract. Gained 1 stone in 6 weeks, great improvement
2	M	21	2 years	*Intestinal symptoms predominating.* Constipation severe (bowels open every 8 days), shivering attacks, headaches, abdominal colic every night, wakes him up, wind + +. Temp. 96°, pulse 64, purple cyanotic extremities, stocking and glove anaesthesia	−13·4 %	−2·8 %	Thyroid extract. Constipation much improved, no attack, different man
3	F	41	5 years	*Mucous colitis.* Nil stools, sudden onset and offset, generally attacks early morning	−36 %	+5·5 %	Rest, no glandular extracts
4	F	32	3 years	*Nervous colitis, asthma.* Following childbirth. Nil stools, attacks generally at night; both temporarily cured by adrenalin injections	−13 %	—	Hormotone, thyroid extract. No attacks since treatment established
5	M	36	18 years	*Profuse sweating attacks* at night (7 sheets per night in ward), also exophthalmos. Marked tremor, attacks every 2–3 years. Pulse 52, B. P. 96. After 7 weeks' treatment only a few slight attacks. Tremor much less. Exophthalmos much less marked	−22·7 %	+10·1 %	Thyroid extract. Improved greatly. Gained 6 lb. in weight
6	M	12	7 months	*Fainting fits* on getting up in the morning, unconscious 5 minutes, followed by vomiting, then quite fit, wind + + +. After treatment no major attacks, still dizzy feelings	−22·7 %	—	Thyroid extract. Greatly improved
7	M	32	1 year	*Fits.* Concussion 1914, quite well until 1920. First fit November 1920, fell unconscious in road, perhaps a dozen since and almost daily dizzy feelings: often at night about 2. Pulse 50, temp. 97°. Minor attack during examination. P. 50 and pallor	−7·3 %	+7·8 %	Thyroid extract. Excellent result, no fits since treatment established

In Cases 1, 2, and 3 (Table V) of this series, the onset of nocturnal enuresis occurred after what may legitimately be called periods of stress, an attack of appendicitis with appendicectomy in Case 1, scarlet fever in Cases 2 and 3. A similar history could be obtained in several other cases not included amongst these examples. It is also a matter of common experience that this condition is especially liable to appear after excessive fatigue or overwork, and it is par-

ticularly noticeable that the children most likely to be affected in this way are those showing well-marked minor physical characteristics suggestive of endocrine deficiency.

It has been considered possible that this method of examination may prove of value in distinguishing a wider group of individuals suffering from parasympathetic phenomena, the result of deficient sympathetic endocrine activity. It is impossible in this paper to consider this group in detail, but Table VI gives a series of seven cases which illustrate the results of basal metabolism investigations in these individuals. It will be noticed that here again the parasympathetic phenomena are particularly liable to occur during the night or in the early morning. Further, they are remarkably amenable to treatment with glandular extracts, especially thyroid extract. In the first examination the basal metabolism is considerably below the normal level in all these cases. In Cases 2, 3, and 5, where this test was carried out after treatment, it was found that the level of the basal metabolism had been raised, and coincided with a great improvement in the condition.

Some Observations on Normal Subjects.

In the present paper the results obtained have been based on the standards worked out by the investigators mentioned above. In order, however, to check these standards, a few observations have been carried out on patients in whom there was no reason to suspect any endocrine disturbance. These patients were generally suffering from some minor surgical condition, and may be regarded as average normal individuals. The few cases I have investigated corroborate the results obtained by other observers. Indeed, they tend to show that in the normal individual, examined under the conditions of my experimental work, the average basal metabolism is on the whole above rather than below the normal base line quoted in the literature. This, of course, strengthens the views expressed in the present paper, as probably the slight minus results are really more marked than they appear to be. The figures obtained in this group of individuals are given in Table VII.

TABLE VII.

	Sex.	Age.	Remarks.	B. M. R.
1	M	37	Normal	+10·9 %
2	M	25	Normal	+7·8 %
3	M	18	Normal	+12·9 %
4	M	13	Normal	+13 %
5	F	29	Normal	+5·4 %
6	M	44	Inguinal hernia	+6 %
7	M	30	Haemorrhoids	+3·7 %
8	F	38	Varicose veins	+3·6 %
9	M	14	Chilblains	+13·5 %
10	M	14	Dyspepsia	+8·75 %
11	F	14	Old tubercular knee	+8·8 %
12	M	29	Recovered dysentery	+9·3 %

It is, of course, not claimed that the present series of basal metabolism estimations afford any definite proof of the correctness of the hypothesis which has just been put forward. In fact, it is realized that the interaction between the various chemical and nervous factors concerned is so delicate and complex that the explanation of the resulting phenomena is almost certainly less simple than the one which is here propounded. At the same time, this investigation opens up a line of thought which seems to present a useful working basis for the investigation of these obscure conditions.

Summary.

1. The results of the present series of basal metabolism estimations in gross disorders of the thyroid gland agree with those of other observers, and indicate the great value of this method of examination in estimating the degree of glandular activity prevailing at the time of observation; the method also provides a reliable guide as to the success of various methods of treatment.

2. In gross disorders of the pituitary gland, results more or less analogous to those found in the case of the thyroid have been obtained, and have proved of equal value in the diagnosis and treatment of these conditions.

3. Estimations of the basal metabolism at the physiological epochs of life in individuals, especially women, who show any tendency to thyroid or pituitary instability, are of great value in confirming any early abnormality, and indicate the lines for suitable treatment.

4. In children suffering from nocturnal enuresis the value of basal metabolism estimations has been established. An indication is obtained as to those likely to derive benefit from treatment with glandular extracts.

5. In an investigation of patients suffering from phenomena which are apparently due to parasympathetic over-excitability, a group of cases has been isolated showing a subnormal basal metabolic rate. These individuals benefit greatly from organotherapy.

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